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Cushing's Syndrome without Adenomatous or Hyperplastic Changes in the Pituitary Body or Adrenal Cortices and Complicated by Alkalosis: Report of Case with Necropsy

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THOMPSON and Eisenhardt's[1] recent review of Cushing's syndrome[3] clearly indicates the advisability of recording further examples of this condition in which detailed clinical and pathologic studies have been conducted. We are therefore reporting data on the following case. The absence of adenomas, neoplastic, or hyperplastic changes in the pituitary body, thymus or adrenal cortices and the associated alkalosis that was present during the life of the patient are elements of additional interest. A similar case was described by Ulrich (2) and in this instance detailed chemical studies were made by McQuarrie and his associates (3).

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[3] The term "Cushing's syndrome" is used here in the sense suggested by Kessel and refers to the clinical picture described by Cushing; namely, hirsutism, amenorrhea or impotence, plethoric obesity, purplish striation, hypertension and osteoporosis. Cushing's syndrome has been found in association with basophilic tumors of the anterior lobe of the pituitary body, neoplasms of the adrenal cortex and hyperplastic lesions of the adrenal cortices (sometimes in conjunction with thymomas). Cases have also been described in which findings at necropsy have been extremely meager. In nearly all instances, Crooke's hyaline changes of the basophilic cells of the anterior lobe of the pituitary body can be found. The term "Cushing's disease" refers to Cushing's syndrome that has occurred in association with a basophilic adenoma of the pituitary body.

REPORT OF CASE

The patient was a white woman, aged twenty-seven years, who came to the Mayo Clinic August 25, 1941. She gave as her chief complaints "weakness and high blood pressure."

The patient stated that in 1938 her menstrual periods, which previously had been normal, suddenly ceased for a period of seven months, after which time they spontaneously recurred. There were no hot flushes. In October, 1939, her menses again had stopped and at the same time she noticed a progressive, general fatigue and weakness of the legs. This weakness soon became so pronounced that she needed assistance when climbing stairs. In November, 1939, she had become mentally deranged to such an extent that it became necessary to confine her to a mental institution. At the end of five months, her mental symptoms disappeared rather abruptly. Concomitantly she began to have headaches, which were persistent and which she described as a "tight skull cap on the head." On several occasions, her systolic blood pressure was found to be as high as 270 mm. of mercury but usually it was found to be around 175 mm. In January, 1940, sugar had been discovered in the urine. At first 40 units of insulin were required daily; two months later, the glycosuria had decreased to such an extent that it could be controlled by diet alone and after October, 1940, even dieting no longer was necessary. While the patient was in the mental hospital, hair started to grow on the face, especially the upper lip, legs and pubo-abdominal region. Simultaneously the distribution of body fat changed. The arms and legs became thinner than they had been, whereas the face, shoulders and abdomen seemed to become more obese. Striae appeared on the hips. In May, 1940, after treatment with stilbestrol, her menses had recurred and remained fairly normal thereafter until July, 1941, one month prior to admission to the Clinic, when uterine bleeding occurred intermittently for several weeks.

FIG. 1. Side view of the patient, showing hirsutism, striae, "buffalo hump" and other characteristics of Cushing's syndrome.

On inspection the patient presented most of the features of Cushing's syndrome. She had the characteristically thin arms and legs, relatively obese trunk and abdomen and the "buffalo hump" in the upper dorsal region. The face was full and round but not particularly highly colored. Cutaneous striae were present in the posterior axillary regions and on the lateral aspects of the buttocks. Hirsutism was not particularly conspicuous. The patient did have a slight moustache, a masculine pubic-hair line and possibly an excessive growth of hair on the thighs. Acne was noted on the thorax and back. The breasts appeared to be well developed and the clitoris was normal in size. Nothing significant was found on pelvic examination. All of the retinal arterioles were slightly narrowed but otherwise the ocular fundi appeared to be normal. The blood pressure was 190 mm. of mercury systolic and 145 diastolic. The patient weighed 130 pounds (59.0 kg.) and her height was 5 feet 1¼ inches (156 cm.).

For laboratory studies and special examinations refer to table 1.

In order to exclude the possibility of an adrenal cortical tumor, bilateral surgical exploration of the adrenal glands was advised. It was decided that if an adrenal tumor was not found, a bilateral lumbar sympathectomy could be performed with the hope that the severity of the hypertension could be reduced.

Accordingly, on September 16, 1941, the right adrenal gland was explored and found to be normal. The right splanchnic nerve and celiac ganglion were resected. Nine days later a similar operation was performed on the left side. At this operation the left adrenal gland likewise appeared to be normal. Three weeks later the blood pressure was 170 mm. of mercury systolic and 130 diastolic in spite of the fact that the response to induced sweating indicated that

the sympathectomy had been complete.

In February, 1943, the patient returned to the Clinic. During the interim her condition had grown steadily worse. Her menses had ceased entirely, she had become weaker and fatigue occurred more easily. Her legs had begun to swell, she bruised easily and she thought that she was losing her hair. As the result of a trivial accident she had fractured the fifth lumbar vertebra.

On examination all of the manifestations of Cushing's syndrome were more conspicuous than at the previous examination (fig. 1). The striae now were distinctly purplish. The arms and legs were thinner than they had been and the muscles had wasted. There was evidence of osteoporosis in the roentgenograms of the skull and spinal column. The blood pressure was 190 mm. of mercury systolic and 150 diastolic. The appearance of the ocular fundi had changed for the worse and was of the type seen in malignant hypertension. The right optic disk was elevated 2 diopters. Surrounding it were hard absorbing exudates. Peripherally there were many cotton-wool exudates and scattered hemorrhages. The left optic disk was flat but the other changes noted on the right were present. In each retina the arterioles were narrowed and spastic and post-spastic constrictions could be seen. The heart had enlarged to the right and the left. When, while the patient was in the hospital, she stooped to pick up a light traveling bag, she was seized with a severe pain in the back and was

TABLE 1. LABORATORY FINDINGS

	1941	1943
Urinalysis		
Specific gravity	1025	1015
Reaction	Alkaline	Alkaline
Albumin	Grade 1[1]	Grade 3[1]
Sugar	0	Grade 2[1]
Microscopic examination	Occ. R.B.C. Pus grade 1[1]	Pus grade 1[1] Few hyaline casts
Hematology		
Hemoglobin	15.4 gm.[2]	12.2 gm.[2]
Erythrocytes	4,410,000[3]	3,820,000[3]
Leukocytes	10,900[3]	17,900[3]
Platelets	—	123,000[3] 124,000[3]
Coagulation time	—	5½ min.
Prothrombin time	—	17 sec. (normal 18 sec.)
Blood chemistry		
Urea		54[4]
Sugar	77 mg.[2]	149 mg.[2]
Hematocrit	—	45.6 per cent of cells
Sodium	—	319 mg.[5] (138.8 m. eq. per L.)
Potassium	—	10 mg.[5] (2.6 m. eq. per L.)
Chloride	—	333 mg.[4] (93.9 m. eq. per L.)
Carbon dioxide content	—	78.1 vol.[4]
Protein	—	6.8 gm.[5]
Miscellaneous		
Exton glucose tolerance test	Blood sugar / Urine sugar	
Fasting	77 mg.[2] / 0	—
½ hr.	194 mg. / Trace	—
1 hr.	313 mg. / Grade 1 to 2[1]	—
Roentgenograms		
Thorax	Normal	Pulmonary congestion. Marked cardiac enlargement. Edema
[illegible]	Normal	Generalized osteoporosis
[illegible]lumbar segment of spinal column	Normal	Compression fracture body of fifth lumbar vertebra
17-Ketosteroids	8.29 mg. per 24 hr.	9.6 mg. per 24 hr.
Urine estrin	—	17 R.U. per 24 hr. (Frank technic)
Flocculation test for syphilis	Negative	—

[1] On the basis of 1 to 4, in which 1 represents the mildest and 4 the most severe condition.
[2] Per 100 cc. of blood.
[3] Per cubic millimeter of blood.
[4] Per 100 cc. of plasma.
[5] Per 100 cc. of serum.

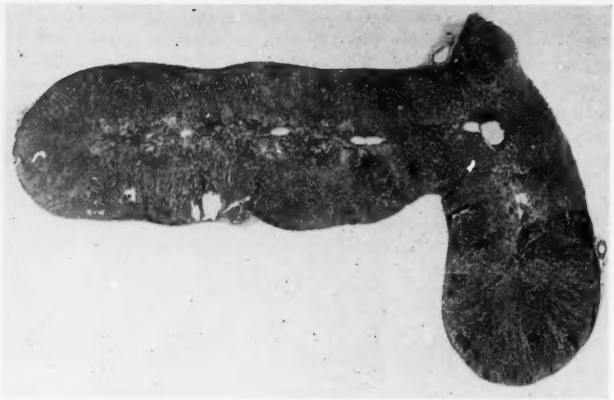

FIG. 2. Adrenal gland of the patient. The gland is normal (×6).

found to have fractured the tenth thoracic vertebra. Death occurred from pulmonary congestion and pneumonia a few days later. During the latter months of her illness the diabetes had practically disappeared in the sense that neither insulin nor dieting was necessary.

Necropsy was performed twelve hours after death. The gross anatomic abnormalities that were encountered were disappointing in that they did not shed light on the cause of the patient's illness. As one would expect, the heart was greatly enlarged and weighed 500 gm. There were mural thrombi in both ventricles. The coronary vessels were small and not sclerotic. The aorta was thin walled and hypoplastic. It measured 1.3 cm. in diameter. Two-thirds of the tail of the pancreas was destroyed by an infarct resulting from a thrombus, lodged in a small artery, producing fat necrosis. Most of the islands of Langerhans in the remainder of the pancreas appeared normal, although a small percentage of them contained hyaline masses.

The adrenals appeared normal in every respect (figs. 2 and 3). Their combined weight was 15.2 gm. There was no microscopic evidence of hyperplasia.

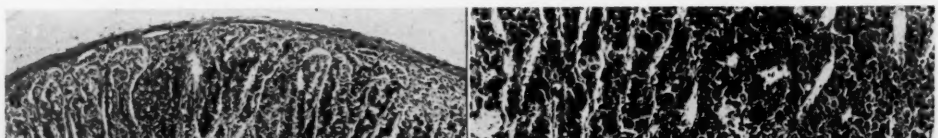

FIG. 3*a* and *b*. Adrenal cortex of the patient. The cortex is normal (*a*, ×35; *b*, ×100).

The Ponceau-fuchsin stain recommended by Broster and Vines for the demonstration of androgenic tissue gave a negative reaction. The tissue, however, was fixed in formalin. The uterus was small with hypoplasia of the myometrium. The scanty atrophic endometrium was in the early proliferative phase of the menstrual cycle and contained a few cystic glands. The ovaries were in process of involution. Numerous atretic follicles were present in the atrophic ovaries but corpora albicantia and remnants of corpora lutea represented evidences of previous function. The breasts were atrophic. An increase of fibrous tissue distorted the ducts. Sections taken from the thymic region failed to reveal any thymic tissue.

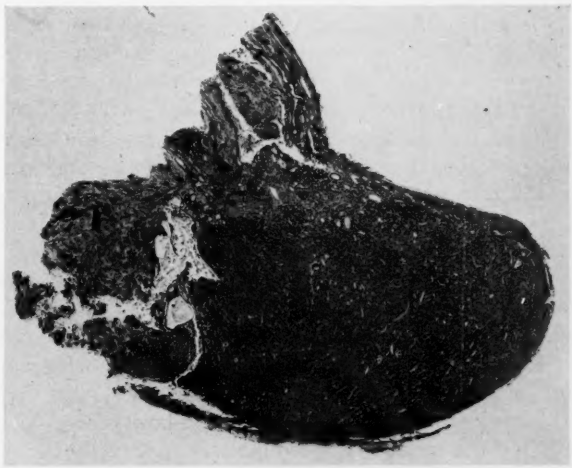

FIG. 4. Pituitary of the patient. The gland is apparently normal (×9).

The thyroid was normal in size and shape and was composed of normal acini with an abundance of colloid. The parathyroids were not studied.

The ribs, vertebrae and skull exhibited moderate osteoporosis. The bone marrow was normal.

The brain was normal except for slight generalized swelling. The spinal cord showed hydromyelocele in the lower thoracic region. The pituitary measured 1 by 1 by 0.5 cm. and grossly appeared normal (fig. 4). No adenomas were found on serial section. The sections stained by the Mallory-Heidenhain method and by Crooke's modification of Mallory's acid-fuchsin aniline-blue method showed the changes described by Crooke (4); namely, the normal basophilic granules were replaced by a dense, homogeneous hyaline cytoplasm, which was of a uniform grayish blue (fig. 5). The degree of change varied from a small region of hyalinization to complete replacement of cytoplasm by grayish blue hyaline material. The hyaline material was found in the periphery as small masses and crescents. In several of the cells the hyaline material contained vacuoles. The nuclei of the basophilic cells were pale and enlarged. An occasional cell contained granular debris. Mitotic figures were absent.

COMMENT

As stated in the introduction, the patient's illness could not be attributed to any demonstrable gross or microscopic anatomic abnormality if one excepts the hyaline changes that were found in the basophilic cells of the anterior lobe of the pituitary body. The physiologic significance of these changes is not known. For reasons that are given in a separate report in this issue, one of us (E.J.K.) believes that these changes are secondary or retrograde rather than "an alternation of fundamental significance in the causation of the syndrome," as suggested by Crooke, and furthermore that the clinical manifestations of the patient's illness were an expression of an abnormal adrenal cortical function of a hypersecretory character, in spite of the fact that there was no histologic evidence to support this view.

The alkalosis of Cushing's syndrome raises a number of complex questions which as yet remain unanswered. Specifically, it is characterized by reduced concentration of the plasma chlorides and potassium, increased carbon-dioxide content and increase of blood pH above normal. Even when searched for routinely in cases of this kind alkalosis is not encountered frequently. Prior

to our experience with the case under discussion, we had observed only a few examples of it among cases of Cushing's syndrome. Our earlier experiences reported four years ago included only three cases. These consisted of one case of thymoma and adrenal cortical hyperplasia, one case of adrenal-like ovarian tumor[4] and one case of Cushing's syndrome of unknown cause. Additional cases have been reported by McQuarrie, Johnson and Ziegler (3) (and by Ulrich (2) as previously mentioned) and by Anderson, Haymaker and Joseph (5). In a series of approximately twenty consecutive cases of adrenal cortical tumor there was not a single instance of alkalosis. Under the circumstances, it was only natural that we felt considerable doubt regarding the part played by the adrenal cortex in the production of these chemical changes. Recently, as a result of two cases, we have had fewer misgivings. The first of these was mentioned by Albright. The second, in which the patient was observed at the Mayo Clinic, will be reported elsewhere. Both patients had Cushing's syndrome associated with adrenal cortical tumors and both both had the specific type of alkalosis under discussion. In our case the alkalosis disappeared without the employment of any corrective measures after the tumor was removed and recurred when the tumor recurred. The evidence of these two cases removes any reasonable doubt that in certain instances, at least, the alkalosis occurs solely as the result of abnormal adrenal cortical function.

From what is known regarding the behavior of the plasma electrolytes in cases of Addison's disease, the character of the alkalosis of Cushing's syndrome is different from what one might suspect. Acute adrenal cortical insufficiency is characterized in part by reduction in the concentrations of plasma sodium, chloride and bicarbonate, and usually by increase in the concentration of plasma potassium. Reasoning by analogy, one might expect a hyperfunctioning adrenal cortical lesion to produce an exactly antithetic electrolyte pattern. This, however, is not what takes place as the concentration of plasma chlorides is reduced in both conditions—otherwise the abnormal electrolyte pattern of Cushing's syndrome is essentially what might be anticipated (table 2, parts 1 and 3). Plasma potassium falls and bicarbonate increases in concentration. The plasma sodium either remains normal or increases[5] in value.

Why should hypochloremia occur in these two conditions whose characteristics are in so many other respects exactly opposite to one another? One can conceive of a retention of bicarbonate causing a reciprocal decrease in chlorides, or conversely, a loss of chloride causing a reciprocal increase in bicarbonate. Such reciprocal relations in the behavior of these two ions have been known and recognized for a long time—the low-chloride, high-bicarbonate electrolyte pattern that occurs after prolonged vomiting furnishing a common example. However, there is no available evidence to suggest that chlorides are lost from the body or that there is any interference with the elimination of bicarbonate so that this ion is retained. In cases of emphysema, bicarbonate is retained in the blood because of hypoventilation and there is a reciprocal decrease in the plasma chlorides. The pH of the blood, however, remains essentially normal. In the alkalosis of Cushing's syndrome, however, the pH of the blood increases. This fact in itself tends to eliminate hypoventilation as an etiologic factor. Furthermore, on clinical examination of the patient one cannot see any evidence of a respiratory disturbance.

There is some evidence to suggest that the particular type of alkalosis under discussion is intimately related to the decreased concentration of serum potassium. In our case of adrenal cortical tumor associated with alkalosis, which was mentioned previously, we observed in some unpublished experiments that the alkalosis could be intensified when the dietary intake of potassium was

[4] Case reported by Edgar Norris.

[5] In the cases reported by McQuarrie, Johnson and Ziegler and by Anderson, Haymaker and Joseph, high values for serum sodium were found.

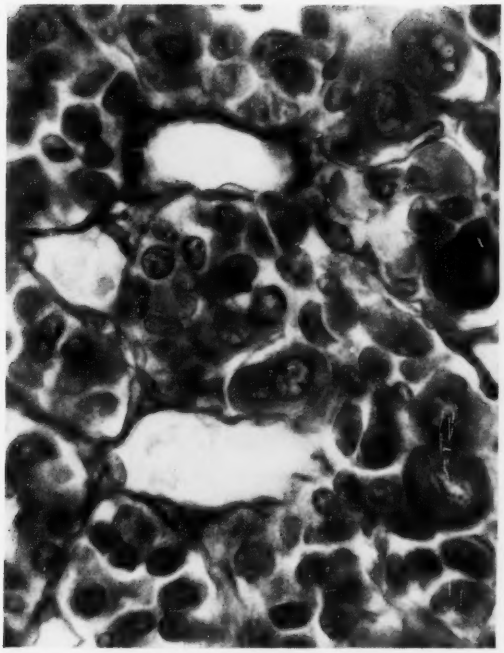

FIG. 5. Anterior lobe of the pituitary of the patient. The basophilic cells show the changes described by Crooke. The cytoplasm is diffusely hyalinized and in some cells contains vacuoles. The nucleus is pale and enlarged (pituitary basophilism) (Crooke's stain, ×800).

restricted. Furthermore, in another case, Willson and two of us (8) were able to rectify the alkalosis by the administration of potassium chloride. Ammonium chloride, on the other hand, appeared to be less effective.

The influence of the low concentration of serum potassium on the electrocardiogram was of considerable interest in this patient. Studies by Dr. Sprague (figs. 6 and 7) were made when the serum potassium was at a

TABLE 2. DATA REGARDING THE BLOOD OF THE PATIENT

Date 1943	Sample	Time	Hematocrit, % cells	Carbon dioxide[1] content, vol. %	Blood pH	Calculated carbon-dioxide, content plasma vol. %	Chlorine	Sodium	Potassium
							Milligrams per 100 cc. plasma and (m. eq. per L.)		
Part 1									
2–10			45.6	Plasma 78.1		78.1	(93.9) 333	(138.7) 319	(2.6) 10.0
2–15			46.7	Whole blood 68.6	7.51	84.7	(89.4) 317	(138.3) 318	(3.0) 11.6
Part 2									
2–19 Control. Potassium citrate, 18.1 gm., orally	1	8:30	42.9	67.7	7.53	82.2	(90.6) 321	(140.0) 322	(3.1) 12.2
	2	11:00	43.9	67.1	7.57	82.5	(91.1) 323	(143.0) 329	(5.6) 21.9
	3	12:30	45.0	67.4	7.57	83.3	(91.1) 323	(143.9) 331	(4.8) 18.7
2–20	4		42.8	65.3	7.51	79.0	(91.1) 323	(139.1) 320	(4.2) 16.5

Part 3

Base		Acid	
	M. eq. per L.		
Sodium	138.3	Chlorine	89.4
Potassium	3.0	Bicarbonate	36.2
Calcium	5.0	Protein	18.3
Magnesium	2.0	Undetermined residue	4.4
Total	148.3		148.3

Base protein calculated according to Peters and Van Slyke, Quantitative Clinical Chemistry, Vol. I, p. 660, on assumption that A/G ratio=2.0

[1] Plasma carbon dioxide content according to line chart, p. 907 on assuming venous blood to be 50% saturated with oxygen.

The results obtained in both of these studies, although encouraging, still leave us very much in the dark. Is the disturbance in potassium indicative of disturbed renal function, altered cellular metabolism or both? In any case, how can the metabolism of potassium influence the behavior of the chloride and bicarbonate ions so profoundly? We do not know the answers.

low level and when it was raised to normal by the oral administration of 18.1 gm. of potassium citrate. Changes in the electrocardiogram included a definite rise in T waves, especially in lead II and CR-2 (fig. 7). These changes were found to be present ninety minutes after the drug was taken and they persisted for nearly three hours. The concentration of the plasma chlorides remained un-

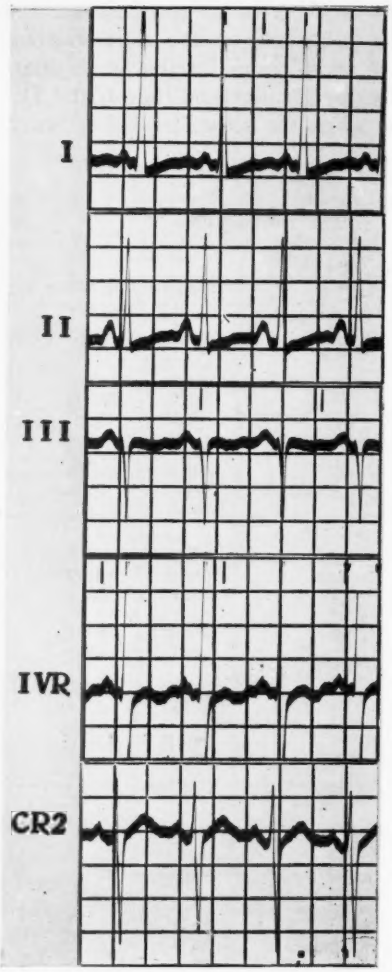

FIG. 6. Electrocardiogram of the patient when the serum potassium was at a low level.

changed and the carbon-dioxide combining power did not increase (table 2, part 2). Similar observations were made on another patient having Cushing's syndrome of undetermined cause. In the latter case the same electrocardiographic change occurred when 12.5 gm. of potassium chloride was given orally. However, in this case because of the chloride ion in potassium chloride the hypochloremia and alkalosis were corrected. These observations prove that the electrocardiographic changes are either the result of the low concentration of the serum potassium or the result of some unknown concomitant factor, which in turn is reflected and influenced by the level of the serum potassium. Those interested in the influence of the serum potassium on the electrocardiogram are referred to the works of Jonota and Weber (9) and of Keith, Osterberg and Burchell (10).

SUMMARY

This report deals with one more instance of alkalosis and low potassium occurring in Cushing's syndrome, three (8, 11, 12, 13)

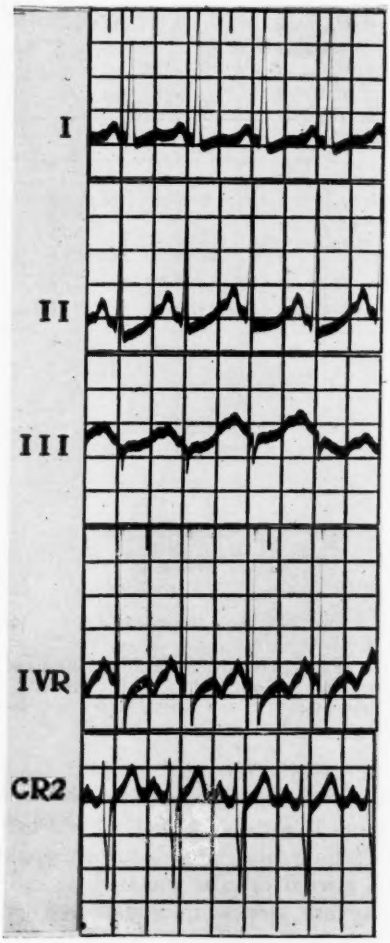

FIG. 7. Electrocardiogram of the patient ninety minutes after ingestion of 18.1 gm. of potassium citrate.

cases having been previously reported from the Mayo Clinic. A minute study of the tissues at necropsy failed to reveal a tumor anywhere or any demonstrable hyperplasia of the adrenal cortex. The administration of potassium citrate brought about definite changes in the electrocardiogram and these changes occurred concomitantly with an increase in the level of the serum potassium.

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The Relationship of "Crooke's Changes" in the Basophilic Cells of the Anterior Pituitary Body to Cushing's Syndrome (Pituitary Basophilism)

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PRIOR to 1930, when Teel and Cushing (1) suggested[1] the possibility of a "hyperpituitary state associated with an adenoma of basophilic elements," basophilic pituitary tumors were considered to be innocuous pathologic curiosities. The following year Teel (2) reported the first case of pituitary basophilism under the title "Basophilic adenoma of the hypophysis with associated pluriglandular syndrome." The symptoms in this case were ascribed to endocrine activity on the part of the tumor. In 1932, in a paper which is now regarded as a classic, Cushing (3) described twelve additional examples of the same pluriglandular symptom complex and attributed it to the hypersecretory influence of an associated basophilic adenoma. In some of these cases he had observed the patient personally and had proved the diagnosis at necropsy. In others, he made the diagnosis from the reported description of the case and predicted correctly that if the pituitary body were re-examined by serial section a basophilic adenoma would be found.

The clinical picture to which Cushing directed attention was no newcomer in medical literature. The idea, however, that it was caused by the secretory activity of a specific type of pituitary tumor was a distinct and novel contribution. Like most new ideas it promptly aroused both unqualified enthusiasm and skeptical opposition. The enthusiasts pointed to the brilliant retrospective diagnoses of Cushing and to the increasing number of cases of proved association of the clinical picture with the tumor constantly being reported. The skeptics were more impressed by the number of cases in which either the tumor occurred without the clinical picture or the clinical picture without the tumor.

Eventually it became clear that neither of these divergent views was entirely correct and that there was considerable truth in both. In support of Cushing's view enough cases were soon recorded to demonstrate that the clinical syndrome and the basophilic tumor occurred conjointly too frequently to be mere coincidence. On the other hand, an impressive number of cases proved beyond any doubt that the bizarre clinical picture was not pathognomic of any particular tumor, pituitary or otherwise. Clinical pictures identical in every major respect and minor detail with that described by Cushing were found to be associated with hyperplastic adrenal cortices and in some instances with complete absence

[1] "Not until the discovery of a hyperpituitary state associated with an adenoma of basophilic elements will it be possible for us to get at the key of those pituitary disorders which primarily cause disturbances of sex and its secondary characters. Undoubtedly such an adenoma will some day be found."

of any gross lesion of the endocrine structures. It was also observed that even when the clinical syndrome did occur in conjunction with the basophilic tumor some degree of bilateral adrenal cortical hyperplasia was also frequently present. More impressive than all this were the two observations that the clinical picture could also be associated with adrenal cortical tumor and that surgical removal of the adrenal tumor was generally followed by the disappearance of the pluriglandular symptoms. If perchance such a tumor recurred after operation, the original clinical picture often did likewise. With this array of evidence to support it the suspicion that the adrenal cortices were in some way responsible for the production of the clinical picture naturally took root.

Cushing himself seems to have had some misgivings regarding the causal relationship of the basophilic tumor to the clinical picture. In his original report with Teel (1) the following sentence occurs: "In ascribing this obscure polyglandular syndrome to a pituitary rather than an adrenal source, I am aware that much might be said in favor of the latter seat of origin." Moreover, although there were at the time comparatively few cases of adrenal cortical tumor on record, Cushing was impressed by the similarity of their associated symptoms to those which he had seen in conjunction with basophilic pituitary tumors. He very definitely anticipated the fact that cases might be discovered which would demonstrate that adrenal cortical tumors could produce the basophilic syndrome *in toto*. If this should prove to be the case, he very logically suspected that a basophilic tumor might in turn stimulate the adrenal cortices to an abnormal degree of secretory activity—which in turn was responsible for the clinical picture (3). In other words, he suspected that in such instances the basophilic tumor would prove to be the remote cause and the secondarily hyperplastic adrenal cortices the immediate cause of the clinical picture.[2]

In a comparatively short time enough evidence accumulated from clinical and experimental sources to convert Cushing's suspicions into a hypothesis, if not an actual theory. Albright (4) has recently summarized this hypothesis as follows:

Deductions from data in the literature

A. Patients with Cushing's Syndrome may present at autopsy either a tumor of one adrenal cortex or hyperplasia of both adrenal cortices; a basophilic adenoma of the pituitary may or may not be present. In cases where the adrenal cortices have been found normal the author questions either the diagnosis or the interpretation of the adrenal histology.

B. A hyperadrenocorticism of a very different kind is likewise produced by tumor of the adrenal cortex or hyperplasia of the adrenal cortices; this second syndrome is designated Adreno-Genital Syndrome and is characterized by rapid growth when it occurs in children, heavy musculature, and the development of male secondary sexual characteristics.

Major Premises

A. Patients with Cushing's Syndrome presumably have some common denominator in the etiology, as it would be unlikely that two entirely unrelated disorders would produce such a combination of clinical findings.

B. Patients with cancer of the adrenals and Cushing's Syndrome presumably are suffering from an hyperadrenocorticism of some kind; ergo all patients with Cushing's Syndrome are suffering from an hyperadrenocorticism.

In the preceding paragraphs I have traced at some length some of the steps that led to the development of the thesis that each and every case of Cushing's syndrome is in reality a case of a specific type of primary or secondary hyperadrenocorticism. Since this thesis has far-reaching implications it is advisable that it be severely scrutinized. The remarks that follow deal with one of the objections that can be, and have been, raised against it.

I have already indicated that gross ad-

[2] "An excess or deficiency of anterior-pituitary hormones, in other words, secondarily affects the function of the adrenal cortex with established certainty, whereas nothing comparable to this occurs in the reverse direction. Hence, if further study should prove that adrenal tumors in the absence of any demonstrable change in the pituitary body may cause a polyglandular syndrome in many respects similar to that under discussion, it may well enough be assumed that, when the same features characterize the syndrome of a basophile adenoma, they in all probability are secondarily ascribable to a hypersecretory influence of adrenal cortex even in the absence of any histologically appreciable abnormality as exemplified by the Parkes-Weber and by the Raab-Kraus cases cited above."

renal cortical lesions frequently are associated with Cushing's syndrome. Thompson and Eisenhardt (5) in a recent review of ninety-eight cases found twenty-two instances of adrenal cortical tumor. If the cases of associated adrenal cortical hyperplasia were also included, the over-all incidence of gross, easily recognized adrenal disease would have been much higher.[3] In the same series of cases the pituitary body in sixty-three instances was made available to the authors for study and comparison with others in the "Brain Tumor Registry" collection. Fifty-eight of these sixty-three pituitary bodies showed a specific type of histologic abnormality. From these data one is forced to conclude that irrespective of what the gross adrenal cortical pathologic changes may be, specific changes in the anterior-pituitary body unquestionably constitute the micropathologic common denominator. These specific micropathologic changes have quite justly become associated with the name of Crooke (6), since he was the first to demonstrate and describe them as they occurred in a series of cases. It is of some interest to note, however, that similar changes were observed in one case by Severinghaus (7) in 1934, one year prior to the publication of Crooke.

Crooke's changes are confined to the basophilic cells and predominantly to the cytoplasm rather than the nuclei. When well marked, they are characterized by cytoplasmic hyalinization, disappearance of the basophilic granules, ballooning of the nuclei, excessive vacuolization, tendency to multinucleation and general enlargement of the cells. This composite picture is often referred to under the term "hyalinization of the basophilic cells." Crooke examined the pituitary body in twelve cases in which frank and severe Cushing's syndrome was present. In this group of twelve cases there were six cases of basophilic adenoma of the pituitary body, three cases of thymic tumor associated with hyperplasia of the adrenal cortices, one case of adrenal cortical hyperplasia without associated neoplasm in the pituitary body or elsewhere and two cases of adrenal cortical tumor. In the six cases of basophilic adenoma of the pituitary body, hyalinization occurred only in the extra-adenomatous basophilic cells. The cells of the tumor proper were unaffected. Crooke also examined the pituitary body in 350 additional cases in which there was no clinical evidence of Cushing's syndrome. In this control group there were only nine instances in which hyalinization of the basophilic cells could be demonstrated and here the degree of hyalinization was slight and the basophilic cells involved were few. Crooke's observations were promptly confirmed by others, notably by Ecker (8) and by Rasmussen (9). It seems reasonably well established, therefore, that with few exceptions conspicuous degrees of basophilic hyalinization occur only in cases of Cushing's syndrome and that in this condition they occur very regularly but not invariably.

Crooke concluded from his observations that although adrenal cortical pathologic changes could, and undoubtedly did, cause virilism, there was no evidence so far as could be demonstrated histologically that "hyperactivity of the suprarenal cortex is an essential abnormality in basophilism." His concluding remarks on the significance of the basophilic hyalinization are of particular interest:

> The only abnormality common to all cases in all groups showing the syndrome of basophilism is the hyaline change in the basophil cells of the anterior lobe, a change moreover which is exceedingly rare and only found in slight degree in subjects not showing the syndrome. It appears justifiable to conclude that this hyaline change is the alteration of fundamental significance in the causation of the syndrome. It has been shown that there is no evidence that the change is a degeneration in the sense of a stage towards the death of the cell. It appears to be confined to the cytoplasm and is probably an expression of altered physiological activity the exact significance of which can at present be only a matter of conjecture.

Except for the phrase "in the causation of the syndrome" there is very little in the preceding paragraph to which one can take ex-

[3] Because of lack of generally accepted gross or microscopic criteria which will enable the pathologist to diagnose adrenal cortical hyperplasia, the exact incidence is conjectural.

ception. Formidable objections can be raised, however, against the view that in every case, regardless of the gross pathologic lesions that may be present, the cause of the syndrome is a disturbance in the function of the basophilic cells of the anterior pituitary.

Since Crooke's views frequently have been tacitly accepted, particularly by clinicians, it is worth while to bring some of these objections to their attention.

In the first place, hyalinization is usually thought of as being indicative of degeneration. This, of course, may not necessarily be the case; nevertheless, its frequent occurrence in association with a large and diversified group of degenerative lesions is difficult to ignore. Be this as it may, to my knowledge it never has been taken to indicate functional overactivity.

Second, as has been mentioned, Crooke's changes have been found in the pituitary bodies of patients having Cushing's syndrome who died because of adrenal cortical tumor. A priori, therefore, the same changes have been present in the pituitary bodies of patients presenting the same clinical picture who were cured by surgical removal of the adrenal tumor. If the "hyaline" change is the alteration of fundamental significance in the causation of the syndrome, the cause should remain in operation after the tumor had been removed. That being the case, it is difficult to understand how such patients could have been cured and remained well for years afterward. One might argue that since the cause of the illness was not eliminated by removal of the adrenal tumor these cured patients eventually will have a recurrence of their symptoms. However, in one of the cases seen at the Mayo Clinic eleven years have elapsed since the adrenal tumor was removed and the patient is still well. Furthermore, it has been my experience that when an adrenal cortical tumor does recur the recurrence usually takes place within a few months after operation.

Third, it has been thoroughly established that when one adrenal cortex is the site of a functioning tumor the fellow gland on the opposite side may be functionally inadequate or even anatomically atrophic. In such cases, if Crooke's interpretation is correct, one has to make the astounding assumption that the etiologic (adrenotropic?) agent manifested histologically by basophilic hyalinization stimulates one adrenal gland so intensely that carcinomatous changes occur and simultaneously represses the activity of the other to such a degree that it becomes atrophic. Such an assumption is so contrary to what is known regarding the responses of endocrine structures to "tropic" agents that it can be dismissed without further comment.

SUPPORT GIVEN BY CROOKE'S CHANGES TO THE THESIS THAT CUSHING'S SYNDROME IS LARGELY AN EXPRESSION OF HYPERADRENOCORTICISM

It is not necessary to conclude that Crooke's changes are in any way implicated in the pathogenesis of the associated clinical syndrome. Rather than being an expression of cause, it is just as logical to assume them to be an expression of effect. In other words, they may indicate a secondary or retrograde, but not necessarily a degenerative, phenomenon, analogous, for example, to the cytologic changes that occur in the anterior pituitary body after castration or thyroidectomy.

When regarded in this manner it is possible to show that Crooke's changes support rather than conflict with the thesis previously mentioned that Cushing's syndrome is largely an expression of hyperadrenocorticism. In the following paragraphs an effort will be made to do this and to suggest a physiologic mechanism by which Crooke's changes might be brought about.

(*a*) *Cushing's syndrome associated with adrenal cortical tumor and Crooke's changes.* There is every reason to believe and no reason to doubt that in cases of this type the adrenal cortical tumor is hyperfunctioning. The enormous excretion of urinary 17-ketosteroids that has been observed in some cases is in itself proof that the tumor is producing excessive amounts of hormonal substances. It is reasonable to assume that this increased secretory output of the tumor might in turn

depress the output of adrenotropic substance by the pituitary body. Histologically this depression might be manifested by basophilic hyalinization. The mechanism outlined previously presupposes that the cause of the adrenal tumor, while not known, is not to be found in the pituitary body. It also presupposes that the basophilic rather than the eosinophilic cells normally secrete this adrenotropic agent. A considerable body of evidence has accumulated to indicate the probable truth of the latter statement.

(*b*) *Cushing's syndrome associated with bilateral adrenal cortical hyperplasia, Crooke's changes and absence of basophilic adenoma.* In cases of this type we assume that the cause of adrenal cortical hyperplasia is unknown and that the hyperplasia is not the result of increased excretion of adrenotropic substance by the pituitary body. Having made this assumption, Crooke's changes would result by the same mechanism outlined in the previous paragraph (*a*). Since it has been discovered that the pituitary body is the source of various "tropic" agents which have the capacity of stimulating other members of the endocrine system, there has been a tendency to attribute the cause of a number of diversified endocrine disorders to the pituitary body. Thus exophthalmic goiter has been attributed to an overproduction of the thyrotropic hormone and so on. I do not think that the evidence thus far presented justifies the sweeping generalization that the pituitary body is the root of all hyperplastic evil. The concept that there may be specific non-pituitary pathogenic stimulating agents is not ready for the scrap heap.

(*c*) *Cushing's syndrome associated with basophilic tumor of the pituitary body and hyperplastic adrenal cortices.* In cases of this type a slightly different sequence of events must be postulated to account for Crooke's changes. I assume first of all that the pituitary adenoma is hyperfunctioning *sui generis* and that its secretory output is not subject to the normal controlling mechanisms of the body. Increased output of adrenotropic agent by the tumor might in turn stimulate the adrenal cortices to hyperfunction. Adrenal cortical hyperfunction would be associated with adrenal cortical hypertrophy and hyperplasia and also would depress the secretory activity of the non-tumorous basophilic cells of the pituitary body. These cells presumably would still be subject to normal controlling mechanisms, whereas the basophilic cells of the tumor would not. In other words, as the tumor functions more and more, the non-tumorous basophilic cells function less and less.[4] Repression of function, as stated elsewhere, might be manifested by hyaline degeneration confined to the non-tumorous basophilic cells.

(*d*) *Cushing's syndrome associated with Crooke's changes and the absence of other gross or microscopic pathologic changes.* Here difficulties are encountered because of the necessity to premise that the adrenal cortices are hyperfunctioning as the result of unknown stimuli and that this hyperfunction is not accompanied by any histologic changes that can be demonstrated by present technics. These two premises having been accepted, Crooke's changes can be explained by the action of the mechanism outlined previously.

COMMENT

The concept that adrenal cortical hyperfunction may occur in the absence of demonstrable histologic changes is a bit disturbing but is not nearly so devastating in its implications as one might think. Analogous endocrine paradoxes have been recognized for a long time and new ones have been unearthed recently. For example, in cases of frank exophthalmic goiter there is sometimes no evidence of hyperplasia whatsoever when the gland is examined microscopically. This fact was observed prior to the now conventional administration of iodine for the management of this disease. Before this type of therapy was introduced, when lobectomy frequently was performed, the first lobe removed might show on examination only colloid changes whereas three months later, when the second lobe was removed, the gland might show fully developed characteristic parenchymatous

[4] In the case of paired endocrine glands this reciprocal relationship is easily demonstrated clinically.

hypertrophy and hyperplasia. The "wildly hyperplastic" thyroid glands that have been encountered since the introduction of potassium sulfocyanate for the treatment of hypertension (10) and of thiouracil (11) for the treatment of exophthalmic goiter furnish additional examples. The same lack of correlation has recently been observed in cases of goitrous cretinism (12), in which the greatly enlarged thyroid of the cretin showed hyperplastic changes. Diabetes mellitus furnishes another example. Certainly few histopathologists would be willing to gage the severity of the disease by looking at the islets of Langerhans.

Returning again to the adrenal cortices, there are now on record well-authenticated cases of adrenal cortical "hyperplasia" associated with pseudohermaphroditism (13, 14) in which the patient died of acute adrenal cortical insufficiency. Finally, hyperplasia of the interstitial cells of the testes associated with unmistakable signs of eunuchoidism has arisen to bedevil and confuse the functionally minded histologist. In short, much as we dislike it, little by little we have been driven to accept the view that with our present relatively crude histologic technics the microscopic appearance of an endocrine structure may be an erroneous criterion of its secretory activity.

Recently a case has been brought to my attention by Drs. Juan Reforzo-Membrives and E. B. del Castillo of Buenos Aires, Argentina, which indicates that basophilic hyalinization is not always the *sine qua non* of Cushing's syndrome. The patient had all the classic signs and symptoms of this disorder. At necropsy all of the endocrine structures were grossly and microscopically normal. Sections of the pituitary body were examined both at Buenos Aires and at the Mayo Clinic and at neither examination could Crooke's changes be discovered. This case proves equally embarrassing to Crooke's contention and to the hypothesis which I have just outlined.

Crooke published his remarks in 1935. These remarks are being written in 1944. Experience with this group of cases has been greatly increased during these nine years. If, nine years from now, the hypothesis I have submitted proves to be as stimulating as that of Crooke has been and still is, I shall be greatly surprised and more than satisfied.

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Studies on the Renal Excretion of Water and Electrolytes in Cases of Addison's Disease

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IN 1938 Cutler, Power and Wilder (1), while working on a quantitative diagnostic procedure for adrenal cortical insufficiency noticed that patients who had Addison's disease voided only small amounts of urine after drinking a large volume of water. These patients were studied under unusual circumstances (1, 2). Their intake of sodium salts previously had been restricted and the dietary content of potassium had been increased to a high level by the administration of potassium citrate. Subsequently it became apparent that the small urinary volumes were not the result of the regimen which the patients were undergoing but that, even under more normal conditions, water did not act as a diuretic agent. This phenomenon was explored further by Robinson, Power and Kepler (3) and eventually became the basis of another diagnostic procedure for Addison's disease which became known as the water test.

Because of its simplicity the practicality of the water test soon became evident and, as our experience with it increased, we began placing more and more reliance on it, particularly as a means of quickly excluding adrenal cortical insufficiency as a cause of illness. Furthermore, from the strictly scientific point of view the test aroused our interest. Why did it work? What became of the water? Was the water absorbed with normal rapidity? Was an abnormal response dependent on a depleted supply of electrolytes and water? Would the test still give a positive result if the patient were previously "saturated" with salt and water? These were some of the questions we asked ourselves. The present study was undertaken with only the last of these questions in mind. We reasoned that if a normal subject were given a large amount of sodium salts and water the volume of his extracellular fluid would be increased. Then when additional water was administered, a large amount of both salt and water would be available for excretion. It was questionable whether or not the Addisonian patient would respond in the same manner. If we could demonstrate that he did not, the difference in his response might be utilized to diagnostic advantage. To anyone who has seen a patient go into an Addisonian crisis when deprived of salt, the value of a test procedure based on the administration rather than on the restriction of salt is obvious and needs no further comment.

The results that we obtained in our investigation are being presented solely because of their intrinsic scientific interest. They are not being presented as a means of diagnosing Addison's disease. Eventually a procedure such as we employed may be utilized as a di-

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agnostic tool. Before this can be done, however, a much larger series of cases will have to be studied.

SUBJECTS CHOSEN

Eight patients having frank Addison's disease were selected for study (table 1). Seven of these had all the classic symptoms and signs of this disorder. The diagnosis in this group of seven was established by positive responses to the test of Cutler, Power and Wilder and to that of Robinson, Power and Kepler. Typical response to specific hormonal therapy was obtained in each instance. *Case 8* deserves special comment. The patient in this case may or may not have had Addison's disease, depending on what criteria are used in making the diagnosis. The case is included in this series because it is fairly representative of a small atypical group of patients which one of us (E.J.K.) has seen.

Case 8. The patient was a girl, aged six years. For three years she had had progressive pigmentation of the skin, lack of appetite and fatigue. The pigmentation was generalized and pronounced and was deepest over the exposed surfaces and pressure points. In addition there was pigmentation of the creases of the palms and of the gums. Some jet black freckles were present. The urinary excretion of 17-ketosteroids in twenty-four hours was 1.6 mg. Both the water test and the test of Cutler, Power and Wilder yielded negative results. Moreover, deprivation of sodium chloride was tolerated for nine days without the production of a clinical crisis. The patient, however, did become weaker as the deprivation of salt was continued and she improved when treated with Kendall's cortical extract.

The patients in the group represented by *case 8* appear to have Addison's disease. Their response to diagnostic procedures, on the other hand, certainly suggests that they have reasonably good adrenal cortical function. The discrepancy can be explained by postulating a bilateral adrenal lesion which

TABLE 1. CONCENTRATIONS OF SODIUM AND CHLORIDE IN PLASMA OF BLOOD SAMPLE DRAWN ABOUT THREE HOURS AFTER ADMINISTRATION OF WATERS AND HEMATOCRIT IN THE SAME SAMPLE

Subject	Diagnosis	Intake of salt in two day preparation, gm. per kg. per day	Sodium (m. eq. per liter)	Chloride (m. eq. per liter)	Hematocrit, per cent cells
		Addison's disease			
1	Addison's disease	0.4 NaCl	127	96	48.4
2	Addison's disease	0.4 NaCl	142	101	33.8
3	Addison's disease	0.4 NaCl	135	102	37.4
4	Addison's disease	0.25 NaCl and $NaHCO_3$	123	91	38.6
5	Addison's disease	0.25 NaCl and $NaHCO_3$	124	99	28.0
6	Addison's disease	0.25 NaCl and $NaHCO_3$			
7	Addison's disease	0.25 NaCl and $NaHCO_3$	127	92	39.4
8	Addison's disease with good residual cortical function	0.25 NaCl and $NaHCO_3$	139	104	36.7
		Controls			
9	Normal	0.25 NaCl and $NaHCO_3$	144	102	47.8
10	Normal	0.4 NaCl	139	100	49.8
11	Normal	0.45 NaCl and $NaHCO_3$	142	104	42.8
12	Chronic "fatigue"	0.25 NaCl and $NaHCO_3$	140	105	45.4
13	Chronic "fatigue"	0.25 NaCl and $NaHCO_3$	141	108	37.1
14	Chronic "fatigue"	0.25 NaCl and $NaHCO_3$	135	103	44.6
15	Chronic "fatigue"	0.25 NaCl and $NaHCO_3$	140	104	41.0
		Other cases			
16	Renal insufficiency	0.45 NaCl and $NaHCO_3$	139	104	43.8
17	Exophthalmic goiter	0.25 NaCl and $NaHCO_3$	138	103	42.6
18	Anterior hypopituitarism	0.25 NaCl and $NaHCO_3$	137	105	36.0
19	Cushing's syndrome	0.25 NaCl and $NaHCO_3$	137	103	43.5
20	Cushing's syndrome	0.25 NaCl and $NaHCO_3$	139	96	49.7

has not progressed sufficiently to impair function to any demonstrable degree. Alternatively, one may assume that they have acquired some sort of compensatory mechanism which makes them differ from the rank and file. Regardless of what the cause may be, there is no doubt that their physiologic status is different from that of the usual patient having Addison's disease. Consequently they tabolism," different in type from that which occurs in Addison's disease. In this group there were one case of chronic nephritis, one of exophthalmic goiter, two of Cushing's syndrome and one of anterior pituitary insufficiency. The data obtained from the study of this group are included for what they are worth and will not be discussed in detail. One case, however, merits some comment.

TABLE 2. VOLUMES AND CONCENTRATIONS OF SODIUM AND CHLORIDE IN THE NIGHT URINE (*A*) AND THE FOUR HOURLY SPECIMENS OF THE MORNING (*B*, *C*, *D* AND *E*)

Subject	Volume, cc.					Sodium, mg. per 100 cc.					Chloride, mg. per 100 cc.					Na in *A*
	A	*B*	*C*	*D*	*E*	*A*	*B*	*C*	*D*	*E*	*A*	*B*	*C*	*D*	*E*	Na in most dilute morning urine
Addison's disease																
1	242	84	60	52	47	302	318	299	299	312	549	550	562	507	540	1.0
2	725	95	110	70	80	419	472	473	528	493	644	775	732	739	732	0.9
3	380	63	52	47	52	388	461	450	453	479	674	801	831	804	788	0.9
4	300	38	36	32	36	562	552	556	533	569	792	888	893	880	891	1.1
5	293	68	80	70	66	363	378	270	279	318	471	456	345	395	431	1.3
6	275	16	49	37	25	319	267	358	405	372	469	478	530	615	618	1.2
7	1,390	53	112	205	60	245	259	239	253	322	363	351	328	331	418	1.0
8	195	275	130	44	24	307	102	113	305	411	449	171	177	448	526	3.0
Controls																
9	500	300	812	132	102	404	128	65	399	537	507	193	86	533	729	6.2
10	240	330	355	270	135	636	110	123	262	424	922	203	199	393	626	5.8
11	430	500	609	100	100	912	102	82	469	620	1,112	138	104	625	786	11.1
12	255	650	780	240	245	641	60	65	201	324	890	99	92	300	464	10.7
13	275	870	395	260	105	601	47	59	156	389	793	77	93	234	580	12.8
14	220	680	675	230	150	503	53	66	204	264	685	79	97	308	386	9.5
15	152	294	580	336	388	733	65	60	66	80	1,030	93	88	96	129	12.2
Other cases																
16	430	90	359	150	82	546	307	94	197	320	850	549	158	359	233	5.8
17	950	385	475	450	490	258	107	110	158	207	317	154	158	232	285	2.4
18	568	86	202	228	204	465	370	179	182	231	665	589	284	268	327	2.6
19	660	770	640	195	130	399	67	74	275	366	464	92	101	397	497	6.0
20	590	585	590	230	195	422	119	106	159	192	543	164	143	225	274	4.0

respond to diagnostic test-procedures in an atypical fashion and might be expected to respond differently to saturation with "salt and water." This proved to be true in case of patient under discussion (table 2).

Among the subjects used as controls, three were considered to be normal and four others who complained of chronic fatigue had no evidence of organic disease.

Five additional patients were selected because of the possibility that they might show some disturbance of "salt and water me-

Case 18. The patient was a man, aged forty-two years, who complained of weakness. He was impotent. He had waxy pallor, soft skin, sparse beard, a feminine pubic hair line and almost no axillary hair. The basal metabolic rate was −2 per cent. The glucose tolerance curve was flat. The urinary excretion of 17-ketosteroids per twenty-four hours was greatly reduced (1.4 to 4.9 mg.). Primary hypogonadism was considered in the diagnosis but seemed to be excluded by the absence of excessive amounts of gonadotropic substance in the urine.[2] On roentgenologic examination of the skull the sella turcica appeared normal.

[2] Determination made by Dr. Carl Heller, formerly of Wayne University, College of Medicine, Detroit, Michigan.

In short, the diagnosis of anterior pituitary insufficiency seemed reasonable but not incontestable. Assuming that the diagnosis of hypopituitarism was correct, some degree of secondary cortical insufficiency may also have been present.[3] This in turn could account for the abnormal pattern of the "salt and water" excretion of the patient.

PROCEDURE

The procedure employed was somewhat similar to that used by Cantarow (6) in his studies on Cushing's syndrome and consisted essentially of two periods which together lasted a total of fifty-two hours. If specific treatment with desoxycorticosterone acetate or cortical extract had been employed, it was discontinued one day before beginning observations. During the first or preliminary period of two days the subject ingested a large amount of sodium salts. During the second period the subject was given a large amount of water to drink and the urinary excretion of water, sodium and chloride was studied. Details of the procedure were as follows:

1. *Period of preparation.*—Food was allowed as desired. Water in the amount of 20 cc. per kilogram of body weight was taken throughout the day. In some instances sodium chloride, 0.4 gm. per kilogram per day, in others, a mixture of sodium chloride and sodium bicarbonate,[4] 0.25 or 0.45 gm. per kilogram per day, was administered orally in four divided doses daily, one each with breakfast, dinner and supper and at 10 p.m. during two consecutive days.

2. *Collection of urine.*—Collection of urine began the night of the second day. At 10 p.m. the subject voided and discarded the urine. Immediately after voiding, the last dose of salt was taken with approximately 200 cc. of water. The subject did not eat or drink anything thereafter. All urine voided after 10 p.m. to and including that passed at 6:00 a.m. of the third day was saved. This specimen was labeled *A* and hereafter is referred to as the "night specimen."

Breakfast was withheld on the morning of the third day. The subject remained in bed. At 6:00 a.m., 15 cc of water per kilogram of body weight was given within fifteen to thirty minutes. All urine passed thereafter until 8:00 a.m. was discarded. At 8:00 a.m. the subject again voided and discarded the specimen. Fifteen cubic centimeters of water per kilogram of body weight was again given as rapidly as the subject could drink it. At 9:00 a.m., 10:00 a.m., 11:00 a.m. and 12:00 m. the subject voided. Each specimen was saved and labeled respectively *B*, *C*, *D* and *E*. These four specimens are hereafter referred to as "morning specimens." Venous blood from the arm was drawn under oil with heparin as anticoagulant at approximately three hours after administration of the second dose of water.

Some objection to this procedure might be raised on the ground that insufficient time had elapsed for the effects of specific therapy to wear off completely. It seems very unlikely, however, for the following reasons, that previous therapy influenced the results that were obtained. First, in our experience previous treatment with desoxycorticosterone acetate rarely reverses a positive reaction to a water test. In that respect our observations are comparable to those of Talbott and his associates (7), who observed that normal renal function was not restored in cases of Addison's disease by specific therapy even when continued over long periods. Second, although the decay curves of desoxycorticosterone acetate and cortical extract have not been worked out completely, clinical experience and experimental evidence lead one to think that the effects of these substances are comparatively evanescent. Third, some of the patients that were studied had not had any treatment whatsoever. Finally, the results that were obtained were comparatively uniform throughout the entire group

[3] It has been demonstrated by Stephens that when the procedure of Cutler, Power and Wilder was applied to a group of patients who had hypopituitarism, most of these patients (seven out of nine) showed increased concentration of chloride in the urine similar to that found in cases of Addison's disease. The recent paper by Gaunt (5) is also of interest in this connection.

[4] The salts were mixed in the proportion of 58.5 gm. of sodium chloride to 33.6 gm. of sodium bicarbonate. This mixture represents approximately the same proportion of sodium to chloride as that in normal blood serum.

irrespective of the therapy previously employed.

METHODS OF ANALYSIS EMPLOYED

Sodium in plasma and urine was determined by the method of Butler and Tuthill (8) (quoted by Peters and Van Slyke). Chloride in plasma was determined by a slight modification of the method of Keys (9), and that in urine by the Volhard-Harvey titration, with the reagents of Peters and Van Slyke (10).

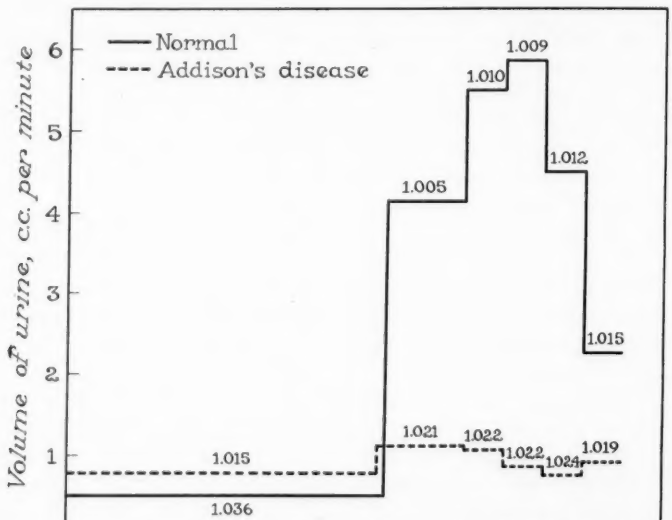

FIG. 1. Excretion of urine before and after ingestion of 15 cc. of water per kilogram of body weight at 6 a.m. and at 8 a.m. Solid line, normal subject (*case 9*); broken line, patient suffering from Addison's disease (*case 3*). The numbers above each horizontal portion of the graph represent specific gravity.

RESULTS

The remarks that follow apply only to the first seven cases of Addison's disease and to the group of seven patients used as controls. *Case 8*, as has been mentioned, was exceptional.

All subjects gained weight when sodium salts were given. The gain in weight of those who had Addison's disease varied from 0.8 to 1.6 kg. This gain implies a retention of "salt and water." Balance studies were not made and consequently the amount of retention was not determined accurately. One can be reasonably certain, however, that any tendency on the part of the subjects who had Addison's disease to go into a negative sodium balance was effectively overcome. In fact, it seems likely that the sodium balance was actually positive because of the large amounts of sodium salts administered, and because most patients having Addison's disease will have normal electrolytic patterns when treated with only 10 gm. of sodium chloride and 5 gm. of sodium citrate.

Administration of water on the morning of the third day produced entirely different responses in the two groups of cases. Most of the patients having Addison's disease showed reduced concentrations of plasma sodium and chloride and decreased hematocrit readings. In retrospect it is unfortunate that we did not anticipate this occurrence and collect data to show the degree of reduction and the time at which it occurred. It is unlikely that such low concentrations were

present before the observations were instituted. None of the patients was in crisis, some had been treated with specific therapy, as has been mentioned, and previous isolated determinations of the plasma chlorides had yielded essentially normal values. Furthermore, the large amounts of sodium salts that were administered should have been more than ample to maintain the plasma sodium and chloride at normal levels. It is reasonable, therefore, to assume that the low concentrations of electrolytes resulted from some abnormality in the absorption and distribution of the "salt and water." Obviously, further studies are necessary to verify or disprove this assumption.

As stated before, we were primarily interested in the urinary excretion of water and electrolytes as it occurred in the two groups of cases. In the patients who had Addison's disease (*cases 1* to *7*, inclusive) the administration of water on the third day provoked almost no diuresis (fig. 1). The volumes of the hourly specimens *B*, *C*, *D* and *E* were small and fluctuated very little and the percentage of administered water still present in the body at the end of four hours was relatively enormous (average 84 per cent, range 74 per cent to 91 per cent). The normal response as exemplified by *cases 9* to *15*, inclusive, was entirely different. Here the hourly specimens were large and variable in amount and the percentage of water unaccounted for was comparatively small. A comparison of the amounts of urine excreted during the night with that excreted during the day affords another striking contrast between the two groups. The patients having Addison's disease with one exception excreted more water during the night than during the day but without exception the normal controls excreted more water during the day than the night. Expressed in mathematical symbols, in Addison's disease $A > B$ or C or D or E, and in all but one case in this series, $A > B + C + D + E$.[5] In normal controls, on the other hand, $A < B + C + D + E$ and in fact A is less than the largest of B, C, D or E.

Equally striking differences between the two groups occurred in the excretion of sodium and chloride, viz.:

1. During the night the normal controls excreted urine that was comparatively rich in sodium. The average value was 633 mg. per 100 cc. (range 404 to 912). On the other hand, among the patients who had Addison's disease, contrary to what one might expect, the sodium concentration in the night urine A was reduced. The average value was 371 mg. per 100 cc. (range 245 to 562).

2. Examination of the data shows that after the administration of water the greatest diuresis almost always occurred in each group during the first two hours after the last dose of water. In other words, specimens B and C are usually the largest of the morning specimens. Comparing these specimens (B and C) in the two groups, it is readily apparent that among the patients having Addison's disease the urinary concentration of sodium was relatively high and invariably was greater than that of the normal subject. For example, the concentration of sodium in the B urine ranged from 259 to 552 mg. per 100 cc. (average 387) in the cases of Addison's disease whereas in the normal group the variation ranged from 47 to 128 mg. per 100 cc. (average 81).

3. In the cases of Addison's disease the urinary concentration of sodium in any one case fluctuated within very narrow limits. In other words, the sodium concentration was fixed. This is apparent when the individual hourly specimens B, C, D and E are either compared with one another or compared with the night urine A. On the other hand, the urine of normal subjects showed wide fluctuations in this respect. This is particularly striking when the B and C urines are compared with either the A or the E urine, namely the night urine and the last specimen voided. As is shown in figure 2, the total amount of sodium in the morning specimens of urine was also less variable among patients who had Addison's disease than among normal subjects. The fixation of the urinary concentration of sodium is also ap-

[5] Using the ordinary water test in a much larger series of cases of Addison's disease, the formula $A > B, C, D$ or E is more accurate than $A > B + C + D + E$.

parent when the following ratio is calculated:

$$\frac{\text{sodium concentration in night specimen}}{\text{sodium concentration in day specimen least concentrated in sodium}}$$

In the cases of Addison's disease the value of this ratio varied from 0.9 to 1.3, whereas values ranging from 5.8 to 12.8 were obtained in the control group.

COMMENT

The data presented, when taken in conjunction with those obtained in previous studies, show the following characteristics: 1. In cases of Addison's disease the rapid ingestion of water is not followed by a corresponding increase of the output of urine. This absence of diuresis is neither the result of restriction of sodium chloride nor correctable by preliminary treatment with fairly large amounts of sodium salts. 2. Patients who have Addison's disease excrete urine having a relatively fixed concentration of sodium and chloride. After the administration of water the urinary concentrations of sodium are greater than normal when hourly specimens having the lowest concentration of sodium are compared with similar specimens voided by control subjects. For example, in table 2 it can be seen that after the administration of water the concentration of sodium in the hourly specimens of urine voided by the patients having Addison's disease did not drop below 239 mg. per 100 cc. (*case 7*, specimen *C*). This should be compared with specimens *B* and *C* among the normal controls. These specimens had the least concentration of sodium in this group. Here the greatest value obtained was 128 mg. per 100 cc. (*case 9*, specimen *B*). 3. Under the conditions of our study the total amount of sodium excreted at any one time by patients who have Addison's disease is not excessive.

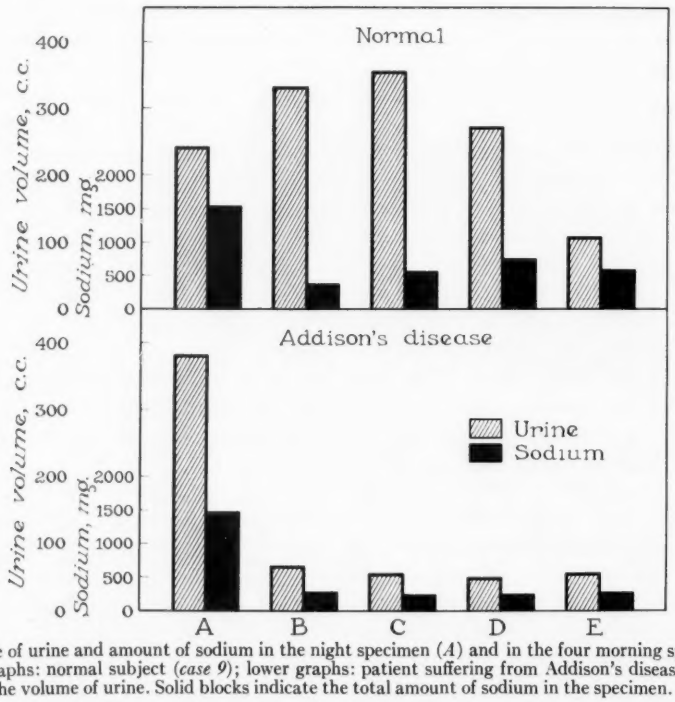

FIG. 2. Volume of urine and amount of sodium in the night specimen (*A*) and in the four morning specimens (*B*, *C*, *D* and *E*). Upper graphs: normal subject (*case 9*); lower graphs: patient suffering from Addison's disease (*case 3*). Shaded blocks represent the volume of urine. Solid blocks indicate the total amount of sodium in the specimen.

It is not surprising that these abnormalities are not well understood, since they are related to such fundamental physiologic processes

as absorption of water, movement of electrolytes from blood to interstitial cell fluid and thence to the cells and vice versa, and excretion of water and electrolytes by the kidney. Superimposed on these are the number and complexity of factors involved in chronic adrenal cortical insufficiency (11, 12). We do have some information, however, that is worth mentioning briefly.

1. *Failure of diuersis.*—Normal water diuresis is preceded by dilution of the blood. This dilution attains its maximum at or about the time that maximal flow of urine begins (13). The dilution is considered to act on the kidney in such a way that renal tubular reabsorption of water from the glomerular filtrate is decreased. Consequently the output of urine is increased. This process is affected by the secretion from the posterior lobe of the pituitary body. There is some evidence to indicate that the effective stimulus to this series of events is dilution of plasma electrolytes rather than dilution of plasma proteins or other substances (14, 15).

In cases of Addison's disease there is some reason to believe that dilution of electrolytes actually does occur after the ingestion of a large amount of water. The data presented in this communication suggest but do not prove this point. In previous unpublished experiments were were able to demonstrate decreased hematocrit, chloride and sodium values after the oral ingestion of water. Regardless of this point, our data do show that in cases of Addison's disease reduction of the concentration of plasma electrolytes does not act as an effective diuretic stimulus.

Extrarenal factors may also interfere with normal diuresis in cases of Addison's disease. The work of Gaunt is of considerable interest in this connection. He showed by direct measurements that when adrenalectomized rats are given in one hour water in amounts approximating 10 per cent of the body weight, the rate at which the stomach empties is decreased and the rate of absorption of water is delayed. It is difficult, if not impossible, to conduct comparable observations on the human subject, so that what evidence we have is indirect. We have no evidence pertaining to the rate of water absorption. We do have evidence (unpublished) showing that when water is given intravenously in the form either of 5 per cent glucose solution or of physiologic saline solution, patients having Addison's disease still exhibit a "positive water test" and fail to secrete urine at normal rates. These observations indicate very strongly that the phenomenon under discussion cannot be disposed of by postulating delayed absorption and that even if the water were absorbed there would still be a delay before it reappeared in the urine.

2. *Fixation of the urinary concentrations of sodium.*—This phenomenon has far-reaching implications so far as the pathologic physiology of Addison's disease is concerned. The data show that in cases of Addison's disease there is an inability of the organism to adjust function (renal or cellular or both) to sudden changes of internal environment.[6] When the normal person is deprived of table salt, the concentration of sodium and chloride in the urine decreases to very low levels. The body retains its stores of sodium chloride tenaciously and the "*liquid milieu intérieur* . . . which surrounds and bathes all the tissue elements" remains almost constant. The story is quite different in cases of Addison's disease. When the patient is deprived of salt, the urinary concentration of sodium chloride remains high, the blood is depleted of its sodium and chloride and the patient "goes into a crisis." Conversely, when large amounts of table salt are given, the normal subject responds by excreting urine highly concentrated in sodium chloride and the "*milieu intérieur*" again is relatively unaffected. In cases of Addison's disease, under the same conditions, the urinary concentration of sodium chloride remains relatively constant and fixed. Attributing these phenomena to disturbed renal physiologic processes one might say that the latitude of renal function is cramped in two directions: the floor has been raised and the ceiling lowered. In clinical practice consequences of this train

[6] Lack of flexibility to meet sudden changes of external environment has long been recognized among patients having Addison's disease.

of events are retention of fluid and pitting edema. These occur when Addisonian patients are treated with excessive amounts of sodium salts only. If desoxycorticosterone acetate is administered simultaneously the results are anasarca, heart failure and death.

Our study was not designed to demonstrate decreased rate of elimination of excessive amounts of sodium salts and the data presented suggest rather than prove this contention. They are much more impressive, however, when considered with the work of others. Greene, David and Johnston (16) showed that after excessive intake of sodium chloride retention of this substance occurred in amounts greater than normal. Failure to secrete a concentrated urine after restriction of fluid was observed in a case of Addison's disease by Willson and Sunderman (17). In the case of adrenalectomized dogs Kottke, Code and Wood (18) showed that the capacity to produce a concentrated urine was lost, although capacity to produce a dilute urine was not seriously impaired.

3. *Total amount of sodium excreted.*—Contrary to expectations, after the administration of water the total amount of sodium excreted by the patients having Addison's disease was not excessive; in fact, the patients actually excreted less sodium per kilogram of body weight than did the normal controls. In the former group the average excretion in four hours was 17.1 mg. per kilogram (range 10.6 to 25.2) whereas in the latter the average excretion was 26.4 mg. per kilogram (range 20.3 to 32.3). These results at first thought seem inconsistent with the generally accepted view that the crisis of Addison's disease following deprivation of salt or withdrawal of hormonal therapy is the result of excessive loss of sodium chloride and water by way of the urine. This inconsistency, however, may be more apparent than real. It will be noted that the patients who had Addison's disease excreted relatively large amounts of sodium even when the plasma sodium was at a low level. When normal subjects are deprived of sodium chloride, total excretion of sodium is much less; this occurs even though the plasma sodium is at a high level compared to that which usually obtains in Addison's disease. Furthermore, from the data here reported, it seems likely that among patients who have Addison's disease urinary excretion of sodium and water proceeds at an even but not excessive rate throughout the twenty-four hours. This seems to take place more or less independently of what the intake of these substances has been, so that if the intake exceeds the loss, retention and edema occur; if the output exceeds the intake, the body stores are slowly but inevitably depleted and crisis follows. The normal subject, on the other hand, speeds up or clamps down on his urinary excretion of sodium and water as the exigencies of the immediate situation demand.

SUMMARY

In cases of Addison's disease rapid ingestion of water is not followed by a corresponding increase of the excretion of urine and the urinary concentrations of sodium and chloride remain relatively fixed.

Some evidence is presented to show that Addisonian patients tend to excrete urine that has a relatively high concentration of sodium even when the concentration of sodium in the plasma is at low levels. However the total amount of sodium excreted in four hours after the ingestion of water was less among patients who had Addison's disease than among normal control subjects.

Subjects who have Addison's disease appear to lose the capacity to make quick excretory adjustments to changes in the intake of sodium and water. The capacity to "concentrate" urine under conditions of water restriction and to "dilute" urine under conditions of water plethora is lacking.

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Hypoparathyroidism of Probable Encephalopathic Origin

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IDIOPATHIC hyperparathyroidism is a rare disorder. To date, Drake, Albright, Bauer and Castleman (1) have reported seven cases with an autopsy in one and have cited eight others. Goadby and Stacey (2), Franco (3), Berk (4), MacBryde (5), Klatzkin (6), and Sevringhaus (7) have each reported one and Emerson, Walsh and Howard (8), two. Kowallis (9) has reported one case and found ten others in the records of the Mayo Clinic—including the three instances of cerebral calcification reported by Eaton and Haines (10). Himsworth and Maizels (11) have reported one case of congenital origin. In the following report, an additional case is presented because of the suggestive evidence of the relationship of the central nervous system to the pathogenesis of parathyroid gland dysfunction.

CASE HISTORY

L. J., a 41-year-old, white, Russian Jewish man, was admitted to the Neurological Service in June, 1937 with the history of repeated convulsive seizures. He had had an attack of measles in childhood, an appendecomy in 1925 and tonsillectomy in 1927 with uneventful recoveries. The family history showed a high incidence of typhus fever, in one case followed by "brain-trouble." His wife had had two miscarriages but there was no history of syphilis. The wife and two children are living and well. His occupation while in Russia was that of a motion picture operator; since coming to this country he has been an electrician for seven years and a furrier for 18 years until the present time. He has been very active in labor union activities, both as speaker and organizer, and has been frequently involved in industrial strife.

Present illness: In 1929 the patient was struck by an automobile, was rendered unconscious for two hours and hospitalized for two days. On discharge he felt perfectly well. Later that year, during the course of a strike, he was struck on the head several times but without immediate sequelae. He continued in good health until 1935. Since then he has noted an increase in stammering and stuttering and increasing difficulty in "finding the correct word." Grasping of the printed word became poor, and memory for recent events began to fail. He also experienced a sense of depression at about this time but could offer no definite explanation for it. In February, 1937, shortly after a nasal polypectomy done at the Bellevue Hospital, the patient suddenly lost consciousness and was said to have had a convulsion with frothing at the mouth lasting a half hour but without biting of the tongue or loss of sphincter control. This was followed by a deep slumber for several hours and a persistent non-radiating pain in the mid-spinal region which kept him bed-ridden for eight weeks. He returned to the out-patient department of Bellevue Hospital regarding this pain in March, 1937; a fracture of the eighth thoracic vertebra was found. Following one such visit, the patient had a convulsive seizure and loss of consciousness preceded by a sensation of weakness, fatigue and occipital headache. This occurred again two weeks later while the patient was lying in bed. This attack was observed and characterized by twitching movements, rolling of the eyes, frothing at the mouth and biting of the tongue —all lasting several minutes and followed by stupor for an hour and a half. He was admitted for one week to Bellevue Hospital where he had three similar attacks. There, a spinal tap and encephalogram were both reported as showing normal findings, but a large psychogenic conflict in the psychosexual field was noted. A diagnosis of idiopathic *grand mal* was made. Thereafter the patient had repeated convulsive seizures at the rate of one a week and was finally transferred to the Montefiore Hospital in June, 1937.

The chief positive findings were referable to the central nervous system; they may be summarized as follows: (1) There was slight unsteadiness of gait with poor associated movements of the right arm;

(2) a slight ataxia in both finger to nose tests with past-pointing to the left with the left hand; (3) nasal and dysarthric speech (nasal polypi?) with stammering; (4) marked myoedema and fibrillations was noted by some, though the electrical reactions were normal; (5) a slight wasting of the left hypothenar eminence; (6) a depression of reflexes in the right upper extremity, but they were elicited on reenforcement; (7) hyperactive abdominal reflexes, and no sensory changes; (8) a bilateral hyposmia (probably due to local pathology); (9) slightly prominent eyeballs with the right pupil being slightly larger than the left, though both were regular and reacted to light and accommodation; (10) a bilateral exophoria; and finally (11) a marked myopia and myopic crescents, without gross visual-field defects.

Mentally, the patient showed a mental tension defect with somnolence and even apathy. Psychologic tests revealed behavior of concrete type with a loss of higher types of ability. The impression was that the patient acted as one with a frontal lobe lesion. He showed the characteristic mental changes of such a patient.

Laboratory examinations: The urine was normal. The erythrocyte count was 4.3 M; the Hb was 84%; the leucocyte count was 7,850, with a differential count of P., 82; L., 17; M., 1; the blood serum values were: glucose 93 mg. per 100 cc.; urea N., 18.4 mg. per 100 cc.; cholesterol, 140 mg. per 100 cc.; total protein, 6.5 grams per 100 cc. (albumin 4.3, globulin 2.2); the chloride as NaCl, 600 mg. per 100 cc.; the CO_2, 59.7 volumes per cent. A five hour glucose tolerance test with 30 grams of glucose orally gave the following values:

Time in hours:	0	½	1	2	3	4	5
Mg. per 100 cc.:	95,	137,	171,	127,	82,	79,	92.

The blood contained no detectable lead, contained 0.08 mg. per 100 cc. of arsenic, and gave a negative Wassermann reaction.

On lumbar puncture, the spinal fluid was clear and the pressure normal. It contained 61 mg. protein per 100 cc. (regarded as elevated). There were 4 lymphocytes per cmm. The Wassermann and gummastic tests were negative. There was no lead. The encephalogram revealed a slight dilatation of the lateral and fourth ventricles and a marked dilatation of the third ventricle. The sella turcica was normal and a small calcification in the region of the pineal gland was noted (Fig. 1 and Fig. 2). The sinuses were normal. A roentgenogram of the chest was normal. The electrocardiogram showed a left axis deviation. The basal metabolic rate was zero. Allergy studies revealed a sensitivity to dust.

Shortly after admission to the ward the patient had a convulsive seizure which was characterized by frothing at the mouth, biting of the tongue, a few clonic twitchings of the lower extremities and unconsciousness followed by fatigue, drowsiness and bilateral frontal headache. No incontinence was noted. There was no preceding aura. The Chvostek sign was

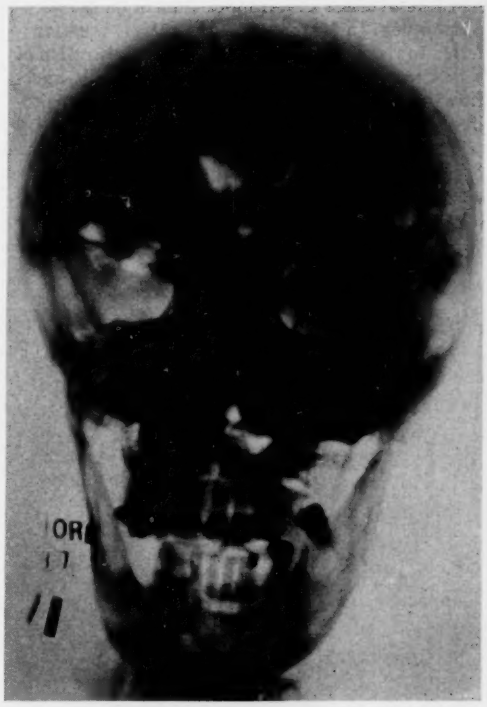

FIG. 1. Encephalographic study reveals marked dilatation of the third ventricle and relatively slight dilatation of the lateral ventricles.

2+. A hyperventilation test made two days later revealed, after eight minutes, a turning of the head to the left, flexion and supination of the left hand with twitching movements of the flexor muscles and extension of the left leg. The labyrinth test results were normal. The opinion at this time was that the patient was suffering from a diffuse disease of the brain, of traumatic origin.

During the next seven months the patient had rare convulsive seizures of the pattern described. Finally, on one occasion, he complained of a cramplike pain in the right hand and foot. The Chvostek sign was found to be positive and the irritability to electrical stimulation increased. The serum calcium and phosphate were found to be 5.1 and 6.0 mg. per 100 cc., respectively. Thereupon, a final diagnosis of hypoparathyroidism was made. It was believed to be the end-result of a diffuse disease of the brain involving particularly the hypothalamic area, in turn affecting parathyroid gland function.

Treatment: During the next year the patient remained on the Neurological Service where treatment consisted of the administration of large quantities of calcium in all forms by all routes of administration, first with a salt-free diet and then with a regular diet, together with Vitamin D, but these treatments had

no effect on either the serum-calcium or on the phosphate levels. In March, 1939, the patient was transferred to the medical service where administration of a diet restricted in phosphorus and sporadic injections of parathyroid extract were begun. This produced a definite progressive reversal of calcium and phosphorus values to a final average level of calcium 8.5 mg. per 100 cc., ocasionally as high as 10.8 mg. per 100 cc. and an average level of phosphorus 4.5 mg. per 100 cc., occasionally as low as 2.5 mg. per 100 cc. Eventually, short periods of treatment with dihydrotachysterol and crystalline Vitamin D, respectively, were given but without significant alteration of the status. During the further course of hospitalization, other observations pertinent to the diagnosis of hypoparathyroidism were made. (1) Roentgenograms of the long bones showed some increased cortical thickening and calcification. (2) Examination of the eyes showed numerous punctate opacities in the deeper part of the cortices of both lenses with a few in the nucleus, which were regarded as characteristic of parathyroid deficiency. Numerous spoke-shaped opacities in the superficial part of the cortex similar to those in the senile or pre-senile cataract were also noted, but the patient was believed too young for this type of cataract.

As to the concomitant effect upon other endocrine glands, the question of adrenocortical insufficiency was raised by the evidence of pigment changes in the skin (characterized by loss of pigment in some areas and the development of brownish pigmentation in other areas, particularly on the left side of the forehead and sides of the neck). A condition of vitiligo was also noted on the hands and on the fingers. The attempt to determine evidence of adrenal insufficiency by the Wilder (12) regime was not fruitful. As to thyroid dysfunction, there were no clinical symptoms of disturbance, and determinations of the basal metabolic rate two years apart were 0 and plus 12, respectively. An eventual disturbance in gonadal function will be mentioned below.

An incidental observation was the development of lipoid pneumonia following the prolonged use of ephedrine "nose-drops" for treatment of a sinusitis.

FIG. 2. Marked dilatation of the third ventricle is seen on lateral view.

The patient was finally discharged to the care of the out-patient department on a regimen of high intake of Vitamin D and calcium and a limitation of the significantly high phosphorus-containing foods.

The patient was observed in the out-patient department for the next year, and except for one instance when the serum-calcium level was depressed to 7.6 mg. per 100 cc. following a rest period of five weeks without medication, the calcium and phosphate levels were relatively well-maintained, the former above 8.5 mg. per 100 cc. and phosphate at about 4.0 mg. per 100 cc. Also, the improved serum-calcium level was accompanied by a rise in total protein from an initial 6.5 gm. per 100 cc. to a subsequent 8.1 gm. per 100 cc. at which time the calcium level was 9.1 mg. per 100 cc. However, the degree of calcium ionization still remained within the hypoparathyroid range according to the chart of McLean and Hastings (13). In spite of the laboratory evidence of improvement, the cataract formation failed to re-

sorb, though the brownish pigmentation on the left side of the forehead did eventually disappear. Other symptoms were increasingly disturbing. The complaints of pains in the arms, legs and lower spine associated with headaches, particularly, in the occipital region, persisted. Periods of mental sluggishness, when the blood calcium tended towards lower levels, were noted. At one time, paresthesias and muscle twitchings were observed in spite of a concomitant serum calcium of 10.1 and phosphate of 4.0 mg. per 100 cc. Ophthalmoscopic examination failed to reveal evidence of increased intracranial pressure. The patient finally began to complain of sexual dysfunction characterized by premature ejaculation and later by impotence. He was last seen on December 30, 1940. He failed to return to the clinic on schedule and on inquiry it was learned that the patient had committed suicide by the inhalation of illuminating gas. No autopsy had been performed.

COMMENTS

There are two aspects of this case that are of interest. The first is the problem of restoration of normal serum-calcium and-phosphorus levels. The second is the question of the possible relationship of the central nervous system to the parathyroid glands.

The first of these entails several observations. First, the restriction of phosphorus for even a short period produced a relatively prompt elevation in calcium in accord with the basic principle of reciprocal relationship formulated by Howland (14) and confirmed clinically (15–18) and experimentally (19–22) by others. Second, the striking effect of even minimal doses of parathyroid extract on calcium and phosphorus levels in contrast to that in normal individuals was in accord with the observations of Aub and associates (23) but met with the increasing resistance noted by others (24–26, 2). Third, the effect of vitamin D and dihydrotachysterol was notable in maintaining normal calcium and phosphorus levels. These observations have already been dealt with exhaustively in the literature and require no further elaboration.

As to the second, more pertinent, aspect, the question of a possible relationship between the central nervous system and the endocrine system in general has been dealt with abundantly of late. Anatomical (29–30), experimental (31–40) and clinical evidences (41–59) have repeatedly affirmed this though it has been predominantly in respect to the pituitary, gonads and thyroid glands. As to the parathyroid glands, this question was previously raised in the reports of cerebral calcification in idiopathic hypoparathyroidism noted by Eaton and associates (27, 10), Albright (28) and Sevringhaus (7). It was generally agreed, however, that the calcification was secondary to, and not the primary etiology of, the disease. Similarly, the report by Altschul and Brown (61) of Wilson's disease with parathyroid insufficiency was not conclusive since autopsy in one of the cases studied revealed marked endarteritis obliterans of the parathyroid vessels, which in itself might have caused the deficiency. Slightly suggestive are the clinical studies by Schneider (62) of constitutional diencephalohypophyseal insufficiency with mild hypocalcemia; while more distinctly so is the report of two cases by Lichtwitz (49), one of diabetes insipidus with subsequent hypocalcemic tetany and the other of "grippe" with subsequent osteoporosis with cyst formation and gonadal atrophy. Neither of these, however, presented any manifest organic cerebral pathology.

In the case of the present report, on the other hand, the coincidence of hypoparathyroidism and organic cerebral pathology, encephalographically indicated, is striking. The interpretation rendered is that the latter represents one of diffuse cerebral tissue injury, particularly within the hypothalamic region and resulting from the original trauma, sustained and manifested by dilatation of, predominantly, the third ventricle as an index of surrounding tissue atrophy. The observation by Vonderhae (60) that, in head injury, multiple minute hemorrhages, particularly within the hypothalamic region may occur, may well explain the pathogenesis in this case. The development of hypoparathyroidism and subsequent sexual dysfunction are regarded as an intrinsic part of the general symptom-complex arising from the underlying cerebral pathology.

The significance of the skin pigmentation that was manifested was also of some concern as to whether this reflected insufficiency of

the adrenal cortex. This possibility could not be confirmed. It is notable that the pigmentation resembled that seen in osteitis fibrosa disseminata (50–52) of which one patient (52), at autopsy, did demonstrate some atrophic changes in the adrenal cortex. It is also of interest that this pigmentation disappeared during the course of therapy.

SUMMARY

A case of hypoparathyroidism with concomitant sexual dysfunction, skin pigmentation, and encephalographic evidence of cerebral damage—particularly within the hypothalamic area—is presented. This appears to be the first instance of hypoparathyroidism coincidental with apparent organic cerebral pathology. The relationship of the two is suggested.

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Review of One Hundred Cases of "Diabetic Neuropathy" Followed from One to Ten Years[2,3]

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THE PRESENT review is presented because this study demonstrated that the so-called diabetic neuritis or neuropathy is not, as is still generally believed, exclusively a peripheral neuritis, but it is also a generalized neurologic disturbance involving the entire nervous system, the central, peripheral and autonomic parts, with special predilection for the peripheral nerves. There is strong evidence to suggest that the neuropathy is only one manifestation of a vitamin B deficiency in diabetic patients, and that the deficiency in most cases is secondary to the metabolic disturbances in diabetes.

We found (table 1) that among the 54 cases that presented a neuritis, only 31 cases had a peripheral neuritis; 26 patients had a myelopathy; nine had signs of encephalopathy alone or combined with a myelopathy and 11 cases had a neurogenic bladder without tabes.

Pain and sensory disorders were the most common symptoms and signs (table 2). Muscular weakness was quite frequent, while muscular atrophy was observed in only 11 cases. Tendon reflex changes were found in only 66 cases. In most of these cases the knee and ankle jerks were either diminished or absent, usually bilaterally. The upper jerks were affected in only one case. Hyperreflexia was seen in five cases. Sphincter disorders, especially of the urinary bladder, were present in 25 cases. Seventeen patients had some gait disorder.

The role of diabetes in the development of the neuropathy is still obscure. Diabetes with its biochemical disturbances, which involve the various organs and tissues, favors the development of a vitamin deficiency. The deficiency is secondary or "conditioned," since it is not usually due to a poor dietary intake. A primary deficiency is possible in those patients who are on a diet inadequate in vitamins. We found 27 cases that were taking a diet adequate in vitamins and minerals at the time the neuropathy developed. On the other hand in 66 cases the diet was inadequate in some of the vitamins and minerals. Insulin was not a factor in the prevention, development or cure of the neuropathy. Loss of weight seems to be important since 58 per cent of the cases had marked weight loss prior or during the development of the neurologic symptoms (table 3). On first glance, table 4 suggests that the condition of the diabetes had no effect on the development of the neuropathy since the latter has been observed in all stages of the diabetes. However, a more careful study of this table brings out some points of interest. Acute manifestations of diabetes were found in 24 cases. In 11 of them the symptoms of the neuropathy became apparent only after the diabetes was already regulated. Rudy and his co-workers (1, 2) have observed that all the

[1] Died February 18, 1945.

[2] Read before the 27th Annual Meeting of the Association for the Study of Internal Secretions, Chicago, Illinois, June 13, 1944.

[3] Aided by a Grant from the Charlton Research Fund, Tufts College Medical School.

TABLE 1. CLINICAL LOCALIZATION OF NEUROLOGIC INVOLVEMENT IN 100 CASES OF DIABETIC NEUROPATHY

	Number of Cases				
	Neuritis	Myelopathy	Encephalopathy[2]	Encephalo myelopathy	Neurogenic bladder without tabes
Symmetrical	17				
Asymmetrical	14				
Generalized	15				
Minimal	8				
Tabes diabetica[1]		12			
Combined system disease		7			
Anterior poliomyelitis		5			
Diffuse myelopathy		2			
Total Cases	54	26	4	5	11

[1] Involvement of posterior columns and roots.
[2] Including cranial nerves.

manifestations of vitamin B deficiency in diabetes develop not only during the acute stage of the diabetes but also soon after the control of the glycosuria and hyperglycemia. It is well known that in debilitating infectious diseases *secondary* vitamin deficiencies, such as pellagra or beriberi, develop not only during the disease but frequently during convalescence (3).

In 17 of our cases the diabetes was uncontrolled, while in 14 cases it was severe and only partially controlled. In all these cases

TABLE 2. LOCALIZATION OF NEUROLOGIC SIGNS AND SYMPTOMS IN 100 CASES OF DIABETIC NEUROPATHY

			Number of Cases								
			Pain	Sensory disorders		Muscle		Ataxia[3]	Tendon reflex changes		Sphincter disorders urinary bladder[4]
				Superficial[1]	Deep[2]	Weakness	Atrophy		unilateral	bilateral	
Extremities	unilateral	upper	2	5	5	3	1	13			
		lower	7	8		9	3				
	bilateral	upper	—	5	28	6	4				
		lower	25	14		13	3				
Generalized	Symmetrical		8	18		3		4			
	Asymmetrical		4			3					
Loss of diminution of reflexes	Knee jerks								3	7	
	Ankle jerks								4	10	
	Knee and ankle jerks								2	34	
	Upper jerks									1	
	Generalized combined										
Hyperreflexia									3	2	
Total Cases			46	50	33	37	11	17	12	54	25

[1] Including paresthesias. [2] Chiefly vibratory. [3] Including gait disorders. [4] Occasionally rectal sphincter.

one may suppose that the disturbed carbohydrate metabolism in some way interfered with the vitamin metabolism and thus brought about the nutritional deficiency. As to the partially controlled, mild cases of diabetes and those controlled for a long time, some had impaired absorption (diarrhea), others had an enlarged liver and some had repeated surgery or a chronic infection with fever. In some cases the dietary intake was inadequate and as a result the vitamin deficiency could also be of primary origin.

It is interesting that two of our cases developed signs of a neuropathy before the diabetes appeared. Jordan (4) claims that all patients with symmetrical peripheral neuropathy should have a glucose tolerance test for latent diabetes, if their urine is free of sugar and the blood sugar value is normal. It

TABLE 3. WEIGHT PRIOR OR DURING DEVELOPMENT OF NEUROLOGIC SIGNS IN 100 CASES OF DIABETIC NEUROPATHY

		Number of Cases			
		Stationary	Gain	Questionable	Loss
Pounds	Less than 5				1
	5– 10				8
	10– 20				10
	20– 30				15
	30– 40				7
	40– 50				7
	50– 60				6
	70– 90				2
	100–120				2
Total Cases		12	2	28	58

TABLE 4. CONDITION OF DIABETES WHEN THE NEUROLOGIC SYMPTOMS FIRST APPEARED

	Number of Cases					
	Before discovery of diabetes	Diabetes				
		just discovered	just controlled[1]	uncontrolled[2]	partially controlled[3]	controlled for a long time
mild		2			23	
severe					14	
acute of various duration		11	6			
acute exacerbation			4	1		
coma			1	1		
without complications				15		
Total Cases	2	13	11	17	37	20

[1] Diabetes controlled—Urine sugar free most of the time, blood sugar always within normal limits, no symptoms of diabetes.
[2] Diabetes uncontrolled—Constant glycosuria and hyperglycemia, symptoms of diabetes present.
[3] Diabetes partially controlled—Glycosuria and hyperglycemia, off and on, no symptoms of diabetes.

TABLE 5. AGES OF 100 CASES WITH DIABETIC NEUROPATHY

		Years							All ages
		Under 20	20–30	30–40	40–50	50–60	60–70	Over 70	
Cases	Males	—	4	2	7	11	10	—	34
	Females	1	—	—	9	22	31	3	66
	Total	1	4	2	16	33	41	3	100

TABLE 6. SIGNS AND SYMPTOMS OF ARTERIOSCLEROSIS IN 100 CASES OF DIABETIC NEUROPATHY

	Arteriosclerosis				
	None	Cerebral	Peripheral	Coronary	Peripheral and Coronary
Cases	71	3	10	9	7

TABLE 7. VITAMIN DEFICIENCY MANIFESTATIONS IN 100 CASES WITH DIABETIC NEUROPATHY

	Number of Cases								
	Deficiency manifestations			Types of deficiency manifestations					
	Absent	Present		Mouth	Skin changes	Pruritus vulvae	Mental changes	Edema non-cardiac	Diarrhea
		Single	Multiple						
Cheilosis				5					
Tongue changes				21					
Gingivitis				2					
Gangrenous stomatitis				1					
Periodontosis				3					
Total Cases	59	20	21		16	15	3	5	5

is possible that the disturbed metabolism in diabetes may favor a vitamin deficiency even in the absence of glycosuria and hyperglycemia.

Arteriosclerosis has been considered by some to be the main cause of diabetic neuropathy. This was suggested by Wilder and Woltman (5) and by Jordan (6) for some cases. Wilder (7) later admitted that a vitamin deficiency may be responsible for the neuritis. Among our cases seven were below the age of 40 (table 5). Only 29 per cent of the cases had definite signs of arteriosclerosis (table 6); three cases had cerebral sclerosis, 10 peripheral sclerosis, nine coronary sclerosis and seven peripheral and coronary sclerosis. The marked improvement in less than six months, observed in 37 per cent of the cases, (table 9) could hardly have been expected if arteriosclerosis were the cause of the neuropathy.

TABLE 8. VITAMIN PREPARATION INTAKE OF 100 CASES OF DIABETIC NEUROPATHY

		Number of Cases	
		When neuropathy developed	During treatment of neuropathy
No vitamins		90	7
Vitamins orally	Yeast	3	27
	Yeast and B_1	1	5
	B-complex	1	11
	Yeast off and on	3	
	Nicotinic acid	2	
Vitamins parenteral and oral	B_1 i.m.[1] and yeast		11
	B_1 i.m.[1] and B-complex orally		22
	B_1 and B-complex i.m.[1]		6
	B_1 and liver i.m.[1]		6
	Liver i.m.[1]		3
	Liver i.m.[1] and yeast		2
Total Cases		100	100

[1] i.m. intramuscularly.

The frequency of manifestations of a deficiency in the various components of vitamin B-complex in diabetic patients with neuropathy is shown in table 7. At one time or another 41 cases showed one or more of the following deficiency signs: cheilosis, tongue

TABLE 9. IMPROVEMENT IN 100 CASES OF DIABETIC NEUROPATHY

		Number of Cases						
Time		Improvement				Progressed	Not followed	Died before vitamin therapy was known
		Marked	Partial	Questionable	None			
Months	Less than 6	37						
	6–12	29						
	12–24	5						
	36	1						
Total Cases		72	7	5	3	3	3	7

TABLE 10. CLINICAL NEUROLOGICAL COURSE IN SEVEN CASES OF DIABETIC NEUROPATHY WITH RECOVERY

		Subjective Symptoms									
		At the onset of neuropathy			When neuropathy fully developed			When neuropathy recovered			
Initials	Age	Pain	Paresthesia	Neurasthenic complaints	Pain	Paresthesia	Neurasthenic complaints	Pain	Paresthesia	Neurasthenic complaints	Condition simulated at onset
H.V.	56	4+	1+	4+	2+	1+	1+	0	0	0	Hysteria
L.P.	67	0	0	0	0	0	0	0	0	0	
D.S.	24	0	4+	0	0	2+	0	0	0	0	
I.C.	60	4+	1+	4+	1+	0	2+	0	0	0	G.I. malignancy Hysteria
L.S.	59	4+	1+	0	1+	4+	0	0	0	0	G.I. pathology
S.C.	72	0	0	2+	0	0	2+	0	0	0	Senility cerebral arterio
H.G.	46	1+	3+	0	1+	1+	0	0	0	0	Peripheral sclerosis

changes, pellagrous skin lesions, or pruritus vulvae.

Vitamin B therapy was used in addition to the control of the diabetes in almost all the cases (table 8). In half of the cases the therapy was both oral and parenteral. In most of them the vitamin treatment was carried out for months.

Complete recovery from the neuropathy was uncertain and slow but it occurred (table 9). Marked improvement was shown by 72 patients under treatment, by 37 of them in less than six months and by another 29 in 6 to 12 months. Some cases showed a progression of symptoms in spite of treatment. Complete recovery with the total disappearance of the objective signs as well as of the subjective symptoms was observed in several cases. Tables 10 and 11 demonstrate the clinical neurological course in seven of the cured cases. One of the cases had a recurrence of the neuropathy. The subjective symptoms usually appeared first and usually cleared up by the time the objective neurologic signs developed. They are therefore not always present together. This would also explain why the neuropathy may be overlooked at the onset and may be mistaken for hysteria, malignancy, etc. The frequent presence of neurasthenic complaints presents the greatest

TABLE 11. CLINICAL NEUROLOGICAL COURSE IN SEVEN CASES OF DIABETIC NEUROPATHY WITH RECOVERY

		Objective Signs											
		At onset of neuropathy				When neuropathy fully developed				When neuropathy recovered			
Initials	Age	Knee and ankle jerk changes	Gait disorders	Muscle weakness	Sensory disorders	Knee and ankle jerk changes	Gait disorders	Muscle weakness	Sensory disorders	Knee and ankle jerk changes	Gait disorders	Muscle disorders	Sensory disorders
H.V.	56	4+	in bed	0	3+	4+	4+	4+	3+	0	0	0	0
L.P.	67	1+	foot drop	4+	2+	1+	foot drop	4+	2+	0	0	0	0
D.S.	24	1+	0	0	2+	2+	1+	0	4+	0	0	0	0
I.C.	60	1+	0	0	1+	4+	2+	3+	1+	0	0	0	±
L.S.[1]	59	1+	0	0	1+	1+	0	0	4+	0	0	0	0
S.C.[2]	72	4+	0	0	2+	4+	0	0	2+	±	0	0	0
H.G.	46	?	2+	2+	1+	1+	2+	2+	1+	0	0	0	0

[1] Later neuropathy recurred.
[2] Also incontinence of feces and urine which cleared up with recovery.

difficulties in diagnosis. On the other hand since psychoneurotic manifestations are a frequent occurrence in thiamine chloride deficiency (8, 9), one of the most probable causes of diabetic neuropathy, these should be of help in the diagnosis. The following case report is presented for illustration.

L. S. (B.I.H. case No. 62306), a 59-year-old woman with a history of diabetes for nine years, was first seen in November, 1941. About four weeks previously she developed an acute exacerbation of the diabetes with oral manifestations of a deficiency of vitamin B-complex, namely a beefy tongue and fissures in the corners of the mouth. She was treated with diet and vitamin B-complex orally. The diabetes and the oral condition showed some improvement. At the same time she developed especially on the right a paroxysmal abdominal pain which increased in severity, and necessitated hospitalization for study. Barium enema suggested the presence of a polyp in the large bowel.

Physical examination revealed a beefy tongue, marked abdominal tenderness and a suggestive mass in the right lower quadrant. The knee jerks were hyperactive but equal and vibratory sensation was absent in both legs. During her stay in the hospital the abdominal pain became more severe and began to radiate into the lower back and down the right thigh, in spite of adequate control of the diabetes. She also developed hyperesthesias in the same regions and numbness of the toes of the right foot. The knee jerks became unequal and greatly diminished. A diagnosis of diabetic neuropathy was made.

She received parenteral injections of thiamine chloride, at first in dosage of 50 mg. per day, then 25 mg. with vitamin B-complex orally. In about five months she began to show marked improvement in her symptoms. She then omitted the parenteral therapy but continued on B-complex by mouth. When examined three months later the hyperesthesia had disappeared completely. There was still a residual of slight pain radiating down the back of the leg. Both knee jerks were present and equal. The left ankle jerk was present while the right was diminished. Vibratory sensation remained absent.

FIG. 1. Shows atrophy of arm.
FIG. 2. Shows atrophy of thigh.
FIG. 3. Shows right foot drop. Photograph taken in the horizonta position.

Comment: This case illustrates a localized neuropathic involvement which responded to vitamin-B therapy after a number of months. The objective neurologic signs were minimal as contrasted to the severity and persistence of the subjective manifestations. The onset of the neuropathy followed the control of an acute exacerbation of diabetes in spite of associated oral treatment with vitamin B. The unusual localization of the initial symptom of pain pointed to intraabdominal pathology, but the subsequent course of this symptomatology made the diagnosis of neuropathy evident. The prolonged requirement of parenteral vitamin administration and the eventual response to the therapy are noteworthy.

Figures 1, 2 and 3 illustrate the diffuse character of the neuropathy. Atrophies of the

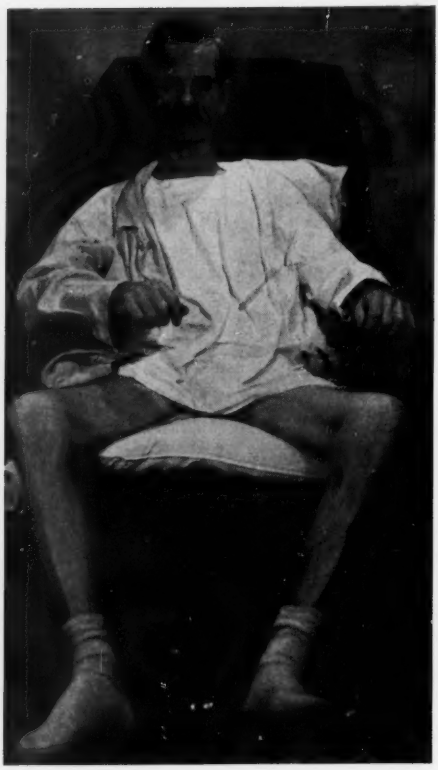

FIG. 4. The patient has paralysis of both legs due to weakness in various muscles with right foot drop.

muscles have been observed in various parts of the body. Weakness and paralysis of the muscles can be confined to one group of muscles or it may be generalized.

SUMMARY

A review of 100 cases of "diabetic neuropathy" is presented. The cases were followed for from one to 10 years. We concluded that diabetic neuropathy is a generalized neurologic disturbance. It is observed not only in the acute stage of diabetes but also soon after the control of the glycosuria and hyperglycemia, and in the chronic and even mild cases of diabetes. This neuropathy develops most frequently in patients over 50 years of age and is preceded or accompanied by marked loss of weight. Symptoms and signs of a vitamin B-complex deficiency are frequently associated with it. The vitamin deficiency is secondary or "conditioned," and it appears to be caused by the disturbed metabolism and at times by an associated chronic infection or other complication. A demonstrable dietary insufficiency is a factor in only certain cases. Complete recovery from the neuropathy is uncertain and slow but it occurs following prolonged therapy with vitamin B and control of the glycosuria and hyperglycemia.

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The Relationship of the Normal and Hyperactive Ovary to Menstruation and to Endometrial Hyperplasia[1]

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ON JANUARY 14, 1909, Frau S. M., aged 26, came into the Woman's Clinic at the University of Heidelberg and submitted to a curettage and suspension of the uterus because of dysmenorrhea, persistent backache and general weakness. She gave the following menstrual history.

The menstrual periods began at 15; at first they were scanty, lasting two days. There was an intermenstrual discharge. After her last (second) delivery she nursed the baby for nine months; then there was a one-day period, followed by nine weeks' amenorrhea and this by a 14-day period of bleeding. Thereafter, every 14 days a five-day to six-day episode of bleeding accompanied by severe pain occurred. In October a moderately profuse bleeding lasted three to four weeks and then five-day to six-day menses continued at 24-day intervals, with above-mentioned symptoms of dysmenorrhea, backache and weakness. After the operation menstruation was regular and painless.

This case is an historical one for several reasons. Foremost is the fact that the curettings furnished an imbedded ovum which was, until the recent epoch-making contributions of Hertig and Rock, the youngest human embryo known. It is of interest to note the date: January 14, 1909; this was only several months after the classical report by Hitschmann and Adler in which they described for the first time the normal endometrial cycle of the human female. Hence it is not surprising that the embryo was not at first recognized as such, or the endometrium as that of early pregnancy or the early "premenstrual" of Hitschmann and Adler. It was Professor J. W. Miller who discovered the ovum, described it briefly in 1913, and sent the five surviving sections to Dr. George L. Streeter for detailed study. The case is one which illustrates the common meeting ground of gynecologist, embryologist and pathologist.

It is of interest to note that after her second delivery the patient passed through a period of amenorrhea followed by episodes of menorrhagia and other pathological symptoms, only to recover spontaneously and completely. Doubtless she attributed her "cure" to the operation, as the surgeon also must have done, for it was not until 1913 that the evidence of her pregnancy was discovered. The endometrium in this specimen is perfectly normal, the same as any premenstrual (pregravid) uterine mucosa 12 days after ovulation. It is an endometrium built up through rapid cell division by about 14 days of estrogenic secretion during the follicular phase of the menstrual cycle, followed by the additive and qualitatively different action of progesterone from the corpus luteum, which brings about secretion of the gland cells. The identical picture may readily be produced in the castrated female monkey and, when there is no uterine pathology, in ovariectomized women also.

Menstruation usually follows this sequence of events: growth of the graafian follicle, ovulation, formation of the corpus luteum, involution of the corpus luteum and finally

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menstruation. Under the leadership of R. Meyer, R. Schroeder and many others the theory arose that there can be no menstruation without ovulation. This theory, which became a dictum to be defended, we now know is not true. Aside from a few human cases that did not "fit" and were disposed of as "pathological," it was found two decades ago by Corner, Allen and Hartman that the female monkey often experiences menstruation without a preceding ovulation, without the presence of any corpus luteum whatsoever, not to speak of a recent one. I have records of three or four thousand menstrual cycles in the monkey in which there was no ovulation, and gynecologists who have studied the matter thoroughly (Hamblen, E. Novak, Rubenstein) now hold that there are few women who ovulate in every cycle. It follows theoretically from this that perhaps progesterone is not necessary for menstruation. Ever since the experiments of the late Edgar Allen in 1927 on the castrated monkey, we have known that estrogen alone is quite sufficient to bring about menstruation, which occurs upon the cessation of the administration of the hormone. Such menstruating uteri are not in the secretory phase but only in the estrogen or "interval" phase. The only steroidal hormone capable of bringing about the secretory phase of the monkey endometrium is progesterone, and there is none to compare with it, although I admit that with huge doses of testosterone the rabbit endometrium has been stimulated more or less toward the pregravid condition.

In a sense, then, progesterone is the most "female" of the hormones, inasmuch as testosterone and other steroids have some estrogenic activity yet cannot substitute for progesterone in the function just mentioned. For the production of the pregravid endometrium progesterone acts, at normal levels of estrogens, synergistically with these. The same sort of action obtains also in case of the mammary gland, but progesterone counteracts the effect of estrogen on the cervix and the vagina of the monkey and presumably of women also.

With the estrogen alone the endometrium may attain maximal thickness, as at the middle of the menstrual cycle or at about the time of ovulation. Cell division continues in both glands and stroma, hence the glands coil more and more to accommodate themselves to the 4–5 mm. thickness of the average secretory mucosa. In these morphological changes the all-important spiral arteries participate. These are longer and more robust and coiled and reach nearer the uterine epithelium (Daron, 1939) when progesterone influence is added to that of estrogen; they are, therefore, better developed in ovulatory than in non-ovulatory cycles. As we shall see presently, it is the unique behavior of the spiral arteries of the primate endometrium which conditions menstruction.

As in all physiological processes, there is a threshold stimulus of hormone for the occurrence of menstruation. Amenorrhea is rightly interpreted as a failure of ovarian endocrines. In experiments on the rhesus monkey the minimal quantity of pure estrogen and progesterone which will cause menstruation in the castrated female has been determined (Allen, Diddle and Gardner, 1936; Corner, 1938; Engle, Smith and Shelesnyak, 1935; Hisaw, 1935; Hisaw and Greep, 1938; Zondek, 1941). Gillman (1942) has data for the baboon, which is well adapted to quantitative studies because of the perineal swellings that arise in response to estrogen and can be measured accurately. As proved by the new studies of Markee (1940) on intraocular endometrial transplants, the minimal dose which brings about "deprivation" bleeding is that which brings about prior growth of the mucosa and the strategic spiral arteries sufficient to afford slack for regression, the *sine qua non* of the menstrual process, as will be explained below.

As to the question, which hormone—estrogen or progesterone—holds primacy in the causation of menstruation, I agree with the majority of gynecologists that it is estrogen. To my notion Markee's observations have clinched this conclusion absolutely, as will be set forth below.

Let us consider the relation of the estrogens to progesterone in other reactions, for

example, their relation to the sex responsiveness in female animals. Estrogen is *the* "heat-" or estrus-producing hormone; and yet progesterone is an important accessory. If one inject a dozen castrated female rats with estradiol, nine of them are certain to come into heat within 24 to 36 hours; progesterone added is more than likely to bring the refractory 20 per cent into estrus. Or if all 12, after being primed with estrogen, receive progesterone, all are likely to come into heat within two to three hours. But after they go out of heat, unlike those receiving estrogen alone, these will be refractory until primed again with estrogens.

The latent period of menstrual flow after estrogen withdrawal and after estrogen-plus-progesterone withdrawal differs widely. If one administers estrogen to a castrated monkey for a period of 10 days she will menstruate seven to ten days after the last injection; but if progesterone is added, the latent period is cut down to two or three days. Similarly, if one removes an ovary containing an active corpus luteum, the monkey (or woman) will bleed in two to three days as against seven to ten days if the ovary contains only a growing or near-mature follicle.

The presence of a corpus luteum affects the titre of urinary estrogens and blood estrogens in the normal menstrual cycle. I have especial reference to the second or premenstrual rise in estrogen at a time when the corpus luteum is beginning to involute. De Allende, Shorr and Hartman (1943) found that the vaginal smear picture indicates that this second rise takes place only in ovulatory cycles. Add to this the growing mass of evidence that progesterone (Everett, 1943, Fraps, 1943) is necessary for ovulation and we may conclude that there is much in the physiological action of estrogens and progesterone still to be elucidated.

In so far as progesterone concerns menstruation, however, we may anticipate the next section by stating (1) that without estrogen it is relatively inert and (2) that, while it may modify the course of menstrual bleeding and some of its outward and superficial manifestations, it has nothing to do with the intimate physiology and *cause* of menstruation. This conclusion follows from the unique contribution of Markee.

THE CONTRIBUTION OF MARKEE

Though published four years ago, Markee's work on "Menstruation in Intraocular Endometrial Transplants in the Rhesus Monkey" has been only too little read and seldom studied by subsequent writers on the subject, especially writers of textbooks. It will probably be several decades before the full significance of the facts presented will be appreciated.

Through the work of Bartelmez (1933), Daron (1936) and Okkels and Engle (1938) the anatomical distinction between the straight basal arteries (supplying the basalis) and the spiral arteries (supplying the functionalis) of the endometrium has become well known. It remained for Markee to elucidate the physiological distinction between the two. Thus, for example, at a certain stage a spiral artery is seen under the binocular to constrict, shutting off the blood supply to the field, which then blanches; but by focusing down one may see the blood travel continuously through the unaffected basal circulation. Having observed intimately hundreds of such localized menstrual cycles in the exteriorized endometria, Markee was able to give us for the first time some significant details of the process of menstruation in terms of the intimate vascular phenomena involved.

First of all in time and importance are the *growth and regression* of the transplants. With the exception of a dip in the curve of growth around the time of ovulation (the dip is, disconcertingly enough, present in non-ovulatory cycles also) growth is progressive from several days after menstruation to two to seven days before the next menstrual flow. The regression amounts to 20 to 65 per cent of the peak volume of the transplant. Such cycles of growth and regression, it may be stated parenthetically, may punctuate periods of amenorrhea, the estrogen level being sub-threshold for menstruation, but the cycles of morphological changes quite definite

(*Case 217*, Plate 1 in Markee, 1940).

The vascular changes preceding menstruation, whether in a normal ovulatory or an anovulatory cycle, or after cessation of estrogen, progesterone or any other steroid, are practically the same and may briefly be described as follows:

1. *Stasis*, with or without general vascular dilatation in the transplant, occurs one to five days before the flow. It begins at the time the mucosa has regressed by 20 to 30 per cent and is apparently caused by a resistance in the spiral arteries. The number of coils in these can be seen to increase as the shrinkage of transplant continues.

This stage is doubtless the phase of congestion known for a century to writers on the subject. The changes in the general milieu of the cells must be profound in consequence of the vascular stasis; hence this may prove to be the critical stage in the preparation for menstruation.

2. *A constriction of the spiral arteries* occurs four to twenty-four hours before the hemorrhage. The blood is thus shut off from the area supplied by the artery and a marked blanching of the field results. Necrosis of the tissues, which ends in sloughing, is most probably due to the anoxia begun during the stage of stasis and completed with the anemia just described. This stage is always present.

3. *Hemorrhage* from capillaries, arterioles and venules. The bleeding may be direct from arterioles temporarily dilated; or from hematomata first formed. Often the blood may be seen to issue by retrograde flow from the veins.

The first blood which pours out does not clot but settles slowly to the bottom of the anterior chamber of the eye from which it rapidly disappears. But if the monkey is frightened, a second hemorrhage from the same arteriole may occur and this blood clots, the fibrin strands hanging suspended from the point of issue for some time.

4. *A cessation of bleeding* takes place through the final constriction of the arteriole. According to Daron this constriction may occur as far back as the myometrium; but in Markee's experiments endometrium only was transplanted.

Markee's chief contribution centers about the pheonomenon of regression. It is the common denominator of menstrual bleeding from every type of endometrium. Observing it in the ocular transplant it is possible to predict the approximate hour of uterine bleeding.

Regression must, however, be rapid to result in hemorrhage. Experimentally it is possible to lower the hormone dosage so gradually as to eliminate the bleeding. Or, one can continue administration of progesterone until the endometrium gradually involutes by "secretory exhaustion" (Hisaw, 1935), without ever causing bleeding (*Case 295*, Plate 2; "*Bon*," Plate 4; Markee, 1940).

With continued daily injection of about 200 Rat Units of estrogen in a castrated monkey, secondary periods of regression and growth with or without hemorrhage occur, which fact argues for an extra-gonadal source of rhythmic stimuli affecting the menstrual cycle (Hartman, 1937; Zuckerman, 1941; *Case 217*, Plate 1, Markee).

PATHOLOGY

Such is the orderly sequence of events in the normal menstrual cycle: growth of the endometrium under the primary influence of estrogens, aided by progesterone; then regression upon sudden failure of the hormone or hormones, this ushers in the above described sequence of changes in the spiral arteries resulting in bleeding into the uterine cavity.

Often, however, the sequence of events breaks down somewhere and this leads to a multitude of menstrual anomalies, most of which are certainly "functional," that is, hormonally controlled. It is believed by most clinicians that the uterus misbehaves because the ovaries are out of rhythm, and these in turn suffer because of the hypofunction or hyper-function of the anterior pituitary gland. The search for the primary cause of menstrual anomalies has been rewarding. But because of the complicated nature of the interrelations of these organs, therapeutic measures are still in the guessing stage, as judged from the mass of conflicting literature on the subject. Some of this

evidence has been ably assembled in a number of first rate American books on endocrine gynecology.

To illustrate the great variety of conditions of ovaries and endometria obtaining in pathological bleedings: these may occur when the endometrium is thin and highly involuted or when it is hyperplastic with dilated glands, ovaries may be large and cystic or reduced in size and "empty." Almost always an unfavorable secretion of estrogens is involved; but sometimes a "mixed" endometrium, reflecting some progesterone activity, is found in a case of anomalous bleeding.

Whether the atrophic condition of certain bleeding endometria is a result of exhaustion from long-time (months and years) of hyperestrinization has not been determined but is theoretically reasonable.

It is safe to say that clinical gynecological hormonology is in a very complicated and chaotic state, and also it is outside my firsthand experience. I agree with Engle that "there is no way to study human physiology other than to study human beings." Yet I believe, that the considerable progress during this century in our basic knowledge of gynecology was accomplished through studies of first the lowly rat and second the rhesus monkey. Significant hints have come from other mammals also—the farm animals and even lower vertebrates. I have already brought in the monkey to illustrate the transition from rat to man; and I venture to call attention to some other pertinent phenomena in these animals.

CONSTANT ESTRUS

Cystic glandular endometrial hyperplasia is now believed to result frequently from an excess of estrogen from cystic ovaries. It seems logical, therefore, to search for similar situations in animals, in an effort to find an experimental subject that might be used to solve this vexing problem.

In the rat a condition known as "constant estrus" may be produced in several ways:

(a) Testes are transplanted into new-born females (Pfeiffer 1936) and the animals are allowed to mature. The testicular secretion changes the pituitary of the now "bi-sexual" female into one like that of the male, which is deficient in the ovulating (luteinizing) hormone. Follicles develop but do not rupture.

(b) The male hypophysis may be utilized in a similar manner by a female (normal, or preferably hypophysectomized) united in parabiosis with a castrated male. In this experiment, again, the male hypophysis is able to bring out only a growth of follicles but no ovulation.

(c) Everett (1943) has found a strain of rats in which females, homozygous for the defect, lack the ovulatory component of the anterior pituitary hormone. These individuals can be made to ovulate by means of gonadotrophins—and also by means of progesterone!

(c) Lastly, I cite Lipschütz's method (1924) of removing a major part of the ovarian substance; the small remainder becomes cystic and hyperactive. This phenomenon will be discussed further.

The above methods (a) to (c) do not lead to pathological changes. As in the estrous rabbit, follicles come and go. There is an inhibitor at work which prevents the follicle from "going wild." A similar condition is seen in pregnancy in which the destructive trophoblast is self-limited, ceasing its erosive action, in man and monkey, about the thirtieth day of gestation when the fetal circulation has been perfected. Would that we understood this inhibitory mechanism—perhaps that understandng would give us the answer not only to the control of chorioepitheliomata but to other neoplasms as well.

The designation "constant estrous" is not, strictly speaking, accurate. In all cases of so-called constant estrus on which I have made observations it has been possible to detect rhythms in the vaginal smear, reflecting endocrine rhythms. This is made especially striking when one employs a good differential stain like that of Shorr (1940). Such a vaginal rhythm is seen in castrated rats receiving estrogen daily (Castillo and di Paola, 1942; Hartman, 1944). I have furthermore repeatedly seen periodic bleeding in castrated monkeys on a uniform daily dosage of estrogen, and this has also been described for women (e.g., Werner and Collier, 1933). Rhythms of

vaginal desquamation during amenorrhea in the monkey are also common. Markee (1940) has described rhythms of growth and regression of the endometrium without bleeding both during injection of estrogen (*Case 321*, Plate 4) and in amenorrhea (*Case 217*, Plate 1).

An extragonadal influence on rhythms in the female genital tract, therefore, seems certain. To discover what this influence is (adrenal? posterior pituitary?) may eventually be of real significance for the explanation and control of uterine pathology.

Severe resection of the ovaries of rat and guinea pig, leaving a minimal amount of tissue, as already stated, results in the production of "cystic" ovaries and, in the hands of Lipschütz and his students, this has caused fibroid tumors in various abdominal organs. That this is the result of hyperestrinization is shown by control experiments with estrogens (Lipschütz, Iglesias and Vargas, 1940). The important consideration for us at the moment is that by the Lipschütz technique, at least in the rat and the guinea pig, a continuous outpouring of estrogen is attained through agency of an ovarian remnant containing follicles only—never a corpus luteum.

The temptation is great to transfer these findings in rats and guinea pigs to man. Indeed it is easy to cite from the literature case after case showing the close association of cystic glandular hyperplasia of the endometrium (one of the few definite pathological entities in this field) with cystic follicles. A well illustrated example is that shown in Figs. 115 and 116 of Hamblen's book. Let us first see what help the monkey can render in these situations.

It is possible to produce in the castrated female monkey a hyperplastic endometrium, even a typical "Swiss cheese" pattern with large doses of estrogen. Some bleeding occurs in the initial stages of the treatment, but this is merely due to congestion; the bleeding is by diapedesis and corresponds to the intermenstrual bleeding of monkeys and of women and has its counterpart in the estrous bleeding of the bitch and the cow.

But in hundreds of female monkeys that have come under my observation, for as long as ten years in some individuals, I have never encountered an example of spontaneous hyperplasia. I have, however, seen a number of cases of continuous light bleeding for periods of from a month to seven or eight months. These were always from highly atrophic uteri. These cases are, of course, as enigmatical as many of those that confront the gynecologist in his every day practice.

In women evidences of hyperestrination have been so often associated with cystic ovaries that the latter may be accepted as the commonest causative agent. Here, too, we get little help from the monkey. I have seen numerous cystic ovaries in the monkey and have followed the rise and spontaneous decline of those which were not removed surgically. The spontaneous recovery has always been permanent; and even in cases in which the ovary was removed with the cyst none ever appeared in the surviving ovary. The following two cases are typical:

No. 57: This fertile female bled lightly from February 10 to April 24, 1931, *when the ovaries were small.* On December 12 of the same year an eleven-day ovum was removed. From the April, 1932 cycle to that of November she harbored an ovarian cyst which varied in size from hazelnut to hickory nut. She recovered spontaneously and permanently.

Monkey *No. 303.* This was a yearling baby when she arrived on September 12, 1931. She was a late adolescent in January, 1935, when a cystic ovary was palpated in left ovary. On January 21, a cyst the size of hazelnut was found. An injection of active progesterone on February 4 failed to reduce the cyst although the animal's sex color faded and the sex swellings collapsed. On June 27, a cyst the size of a hickory nut was found. This continued into October when the size was recorded as that of a walnut. On November 21, 1935, the ovary, then measuring 27 by 21 by 17 mm., was excised. The ovarian tissue was restricted to a thin layer covering the wall of the cyst.

No estrogen was ever recovered from these ovarian cysts. As a matter of fact most follicular cysts removed from women are "empty" of hormone as shown by the careful assays of Watts and Adair (1941), who found that in only three out of 23 cases of cystic ovaries in cancer patients could any estrogen be detected. Normal follicular fluid, of course, never assays high in estrogen content (Allen and others, 1930) but is effective by virtue of the continuity of its secretion. Many follicu-

lar cysts are devoid of granulosa, and these are always free of estrogen. Cystic follicles which are produced in monkeys by injection of gonadotrophins usually have little hormonal action (Hartman, 1942); they are injured structures and doomed to prompt decay.

In the cow, however, there is a condition which should interest the gynecologist. Perhaps this is the experimental animal he is looking for. One of the most frequent causes of sterility in cattle is a cystic condition of the ovaries (Hammond, 1927). According to Shumann (quoted by Hammond) in 70 percent of cows with cystic ovaries the animals exhibit nymphomania as the outward manifestation of estrogen secretion. I learn from Dr. Casida of the University of Wisconsin, who is studying this condition, that he has some evidence which shows that in nymphomaniac cows the endometrium is hyperplastic. Except for the absence of excessive bleeding we have here a near counterpart of endometrial hyperplasia associated with ovarian cysts in women—or in other words, the cow may be an experimental animal which may help to further an understanding of gynecological pathology.

THERAPEUTIC MEASURES

Therapeutic measures aim to change the abnormally functioning mucosa into normally functioning tissue. This has been attempted by aiming the therapeutic measure at the endometrium directly, or indirectly by influencing the ovary.

For direct action one thinks at once of progesterone, because, first, this ovarian hormone is totally lacking when luteal tissue is absent and second, because Lipschütz and his students (1939) successfully counteracted the tumorigenic action of cystic ovaries in the guinea pig by means of progesterone. I gather from the clinical literature, however, that little success has attended the use of this hormone. In the monkey cystic endometria are even easier to produce by adding a slight amount of progesterone to the estrogen than without it.

According to some gynecologists, estrogens are indicated on the theory that in the endometrium an adequate growth stimulus is actually lacking, the hyperplasia seen being the result of the continuity and persistence at a low level of the hormone which is never quite adequate for healthy growth. I read in the literature encomiums passed upon the virtue of high doses of both the natural estrogens and stilbestrol in the control of uterine bleeding (e.g., Karnacky, 1944; McGinn, 1942) and these even followed by normal cycles! Hamblen would imitate nature more closely by establishing a rhythm: 14 days of estrogen treatment followed by 14 days of estrogen plus progesterone.

A stimulation of the ovary in order to cause a rhythm in that organ has been attempted by many. Human chorionic hormone (A.P.L. —anterior-pituitary-like hormone), equine chorionic hormone (P.M.S.—pregnant-mare serum) and extracts of the pituitary (A.P.) either whole or fractionated into the follicle-stimulating hormone (F.S.H.) and the luteinizing hormone (L.H.) are the chief gonadotrophins which are available to us.

The use of A.P.L. is based on experiments with the rat and the mouse in which luteinization of established follicles is readily attainable. The same holds for the opossum; in one such animal treated with A.P.L. I found 440 corpora lutea atretica! I have never seen any luteinization in the monkey ovary, although Engle (1934) and Westman (1938) reported success in this respect (though probably only in follicles already considerably advanced). A.P.L. is not a follicle stimulator. In my hands it acts as a powerful disrupting agent on the ovary. I see no physiological basis for its use as a therapeutic agent in the hyperplasia we are discussing.

P.M.S. has a follicle-stimulating effect and has more promise as a useful addition to the gynecologist's armamentarium. But I am inclined to believe that the natural extracts of the pituitary itself offer the best solution for bringing about ovulation and corpus-luteum formation both in cystic and in hypotypical ovaries for the reason that some progress in this direction has already been made in the treatment of cows having cystic ovaries. In collaboration with Drs. Meyer and McShan (1944) Dr. Casida has succeeded not

only in overcoming the cystic condition but actually in bringing about ovulation, and finally, after artificial insemination, pregnancy in their bovine patients! One gram-equivalent of dry ovine anterior pituitary in the form of crude extract injected once (intravenously) brought about the change. This suggestive experiment in the field of animal husbandry would seem to offer a useful suggestion to the gynecologist.

SUMMARY

In this paper the writer has presented informally what appear to be the more basic facts which must be considered in formulating a working theory on the cause of menstruation. The observations of Markee on the vascular phenomena seen in intraocular endometrial transplants are stressed. Rapid regression of the endometrium with an increased kinking of the spiral arteries and resultant stasis of blood is regarded as the outstanding and epochal contribution of Markee.

Of menstrual anomalies, only one is discussed, namely, metrorrhagia associated with cystic ovaries. A parallel condition is common in nymphomaniac cows which Casida, McShan and Meyer have successfully treated with an extract of whole anterior-pituitary gland.

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EDITORIAL

THYROID DISORDERS IN CHILDREN

CHILDREN are subject to essentially the same diseases of the thyroid gland as are adults but there is some difference in the frequency, manifestations and course of the disorders in the two age groups.

Thyroid disease is less common in children than in adults. Bram (1) found that of 17,000 patients with thyroid disease, 5,000 of whom had exophthalmic goiter, 7 per cent were in children under the age of 16. Among 110,000 hospital admissions to the Pediatrics Department in the Johns Hopkins Hospital (2) there were 102 patients with simple goiter, 46 with cretinism, 20 with acquired hyperthyroidism, 12 with exophthalmic goiter, three with congenital goiter and one patient with thyroiditis. No patient with adenoma of the thyroid was observed. Pemberton and Black (3) found that at the Mayo Clinic, between 1908 and 1943, there were 189 patients with exophthalmic goiter, 70 with adenomatous goiter, 18 with carcinoma of the thyroid and three with thyroiditis.

Essentially all instances of *thyrotoxicosis* in children are associated with *exophthalmic goiter;* adenomatous goiters with hyperthyroidism rarely, if ever, occur in youngsters. Exophthalmic goiters have been known to occur in infancy, but they are distinctly rare before the age of ten; approximately 80 per cent appear in the ten-year to 14-year age period. Girls are afflicted about six times oftener than boys. The disease is no more common in goiter districts than elsewhere. The clinical picture is somewhat similar to that in adults but it tends to be more acute.

Some of the factors which probably are significant in the development of the disease are psychic trauma, overwork, and infections. The commonest manifestations of thyrotoxicosis in children are nervousness, goiter, exophthalmos and tachycardia. Exophthalmos occurs with greater frequency in children than in adults. The nervousness is characterized by marked restlessness, emotional instability and personality changes. A tremor is generally present; it may be fine or coarse and may involve the entire body. This symptom, associated with various nervous manifestations and poor coordination, may pose a differential diagnostic problem in that the combination of manifestations occasionally simulates those of chorea. Tachycardia is generally pronounced but palpitation and dyspnea are somewhat less frequently complained of by children than by adults. The gastro-intestinal symptoms are generally more acute than in adults; nausea, vomiting and diarrhea are not uncommonly present. The loss of weight in active Graves' disease is less marked than in adults; indeed, in about 25 per cent there is a gain in weight during the development of the disorder. General muscular weakness and fatigue develop in the majority of cases. Diffuse enlargement of the thyroid occurs almost without exception; the goiter generally develops early in the course of the disease. The skeletal growth is accelerated and the epiphyseal development is increased; the teeth develop prematurely. Secondary sexual characteristics sometimes appear late and menstruation is delayed. In boys there may be a retardation of sex maturity.

The establishment of a diagnosis of thyrotoxicosis sometimes offers difficulty. Estimations of the basal metabolic rate in children are frequently inaccurate. Because of its high degree of variability in the earlier years, determination of the concentration of cholesterol in the blood is of little aid. A measurement of the protein-bound iodine fraction of the blood is one of the most accurate diagnostic procedures but it is a time-consuming and difficult test. A therapeutic test with iodide or thiouracil is not infrequently of value.

Much variation in opinion has existed concerning the best form of therapy for Graves' disease in children. The performance of subtotal thyroidectomies has been less satisfactory in children than in adults; persistance and recurrence of the thyrotoxicity are more common; and the development of myxedema, should too much of the redundant tissue be removed, is more hazardous because of its interference with the proper growth and devel-

opment of the child. In a total of 109 children operated upon for exophthalmic goiter at the Mayo Clinic (3), since 1921, there has been a mortality of 2.8 per cent. Of 102 patients with satisfactory follow-up data, seven developed recurrences of the thyrotoxicity, one died from hyperthyroidism and 23 developed myxedema or "low basal metabolic rates." Medical treatment was used in 14 of 189 cases of Graves' disease. In follow-up studies the results were described as good in ten, fair in three and poor in one.

It is possible that antithyroid drugs of the thiouracil type may hereafter hold a prominent place in the treatment of hyperthyroidism in children. A remission of the disease occurs with thiouracil but it has not been determined how consistently the effect will be sustained on cessation of therapy.

Hypothyroidism in children appears classically as cretinism or juvenile myxedema, but milder forms of the disease exist. These disorders differ from those of adults in that abnormalities in the rate of growth and in the maturation of the tissues are present.

Although the clinical picture of cretinism is well-defined its rarity in this country has, unfortunately, caused belated diagnoses. Endemic cretinism is sometimes associated with goitrogenesis and results from iodine deficient, and sometimes hypothyroid, mothers. Sporadic cretinism is due to aplasia of the thyroid gland.

The clinical features of cretinism are generally not recognized until the child is from six to 18 months of age. Some of the changes in the skin, hair, subcutaneous tissue, muscle and circulation are similar to those in adult myxedema. However, there are a number of unique changes, such as dwarfism with legs which are short in relation to body length, relatively large head, delayed closure of the fontanels, low forehead, broad base of the nose, widely spaced eyes, puffy eyelids, thick lips, thick tongue, poorly formed and late-appearing teeth, and a short, thick neck. The hands are broad, short and puffy. The abdomen is large and pendulous; the muscle tone is poor and an umbilical hernia is often present. There is mental and physical torpor; sitting, walking, and talking are belated.

Roentgenograms reveal a marked retardation in osseous development. There is an abnormal configuration and delay in the appearance of the epiphyses as well as a retardation in their union with the bone shafts. The diagnosis of cretinism is usually made on the basis of the clinical picture, but the finding of a subnormal basal metabolic rate, hypercholesteremia, and a therapeutic response with desiccated thyroid are of aid. Other types of dwarfism must also be considered in the diagnosis. Mongolism, which is sometimes confused with cretinism, is differentiated by the characteristic changes in the eyes, hypermobility of the joints, uninpairment of growth, greater activity and normal skin.

Treatment with desiccated thyroid should be started as soon as possible. A daily dose of about 32 mgm. is used in the beginning but is increased at intervals of weeks until 96 to 192 mgm is given daily, the goal being to give doses which are just subtoxic. The picture of cretinism can be largely abolished if therapy is started early and given continuously in maximal doses. In general, more success is obtained in promoting normal physical growth than mental development.

Juvenile myxedema resembles adult myxedema in many ways, but there is associated with the former decreased growth and mental development. Diagnosis is usually not difficult, but care should be taken to give maximal treatment with thyroid.

In addition to subjects of cretinism and myxedema there are other groups of patients who have mild manifestations of hypothyroidism the diagnosis of which is often missed. The symptoms may be poorly defined. Sometimes there is a retardation in the mental and physical development, delayed puberty, languor, sensitivity to cold, and slight dryness of the skin. Often they present "behavior problems." The basal metabolic rate is usually normal or a little subnormal. Dorff (4) found that out of a group of 500 patients sent to his endocrine clinic 15 per cent had "masked hypothyroidism." Topper (5) reported that the administration of desiccated thyroid caused marked improvement in a group of children selected because of retardation in mental and physical development. The use of desiccated thyroid frequently offers improvement. In these cases it is possible (a) that too little thyroid hormone is produced, (b) too much hormone is broken down or (c) the end-organ, which is the general body cells, is hyposensitive to stimulation by the thyroid hormone.

Aid in the diagnosis of the hypothyroid cases may be obtained by means of the basal metabolic rate, protein-bound iodine of the plasma,

blood cholesterol and the creatine excretion in the urine. Confirmation may be obtained by the response to treatment with desiccated thyroid, noting the changes in the clinical state, the basal metabolic rate, and serum cholesterol. In cases where the diagnosis of hypothyroidism is suspected but unproved, thorough treatment with thyroid is advisable since the advantages which it offers in promoting growth and development outweigh its possible harmful effects.

Endemic *simple goiters* are common in some areas but sporadic goiters outside the "goiter belts" are uncommon. In these non-goitrous areas simple goiter occurs about six times more frequently in girls than in boys. In goitrous district the incidence of simple goiters increases until the age of puberty; in boys the incidence then declines but in girls the incidence and the size of the gland increases until the age of 17 or 18 and rarely does the goiter disappear. Lack of iodine is of primary importance in the etiology of this type of goiter. The demand of the body for thyroid hormone is also important. A contributory role may be played by infections, excitement and malnutrition. The thyroid gland is uniformly but only rarely markedly enlarged; it is soft and compressible; adenomatous and cystic changes are rare. The basal metabolic rate is sometimes subnormal. Potassium iodide and desiccated thyroid have each been used in the treatment of simple goiters, but the latter is much more efficacious; after several months it often prompts an appreciable reduction in the size of the gland.

R.H.W.

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LETTER

SICKLING TRAIT AND EUNUCHOID HABITUS

To the Editor:

E. A. Sharp and E. C. Vonder Heide have found that sickle cell anemia and the sickling trait are very frequently associated with a "eunuchoid habitus;" that is, with a marked preponderance of the span over the height and of the lower length over the upper length of the body [*This Journal: 4*, 505. 1944]. They state that "inasmuch as the erythrocytic sickling and the abnormal statural development are dominant familial traits it is not irrational to suggest that genetically the anterior pituitary is involved in the causation of both phenomena."

This statement cannot remain unopposed. It has repeatedly been emphasized that "eunuchoid" proportions of the body are not necessarily associated with hypogonadism and cannot be interpreted as being caused by an abnormal pituitary function. (Bauer, J.: *Endocrinol. 8*, 297. 1924). Some Negro races show marked "eunuchoid" proportions and yet are by no means hypogonadal. Nor is puberty in those races retarded. The father ot three siblings with sickle cell anemia and sicklemia, respectively, reported by Sharp and Vonder Heide, had neither anemia nor the sickling trait but had very marked "eunuchoid habitus." It has been shown that genetic factors acting directly upon the epiphyseal cartilages and the growth rate, must be paramount in the development of "eunuchoid" proportions (Bauer, J.: Constitution and Disease. Green & Stratton, New York, 1942). Engelbach's standard tables of body measurements are not valid for Negroes.

If it were actually proven that "eunuchoid" proportions are more frequently encountered in Negroes with the sickle cell trait than in those without it—and this has not been done yet—it would only mean a genetic relation of the two characteristics, that is, either pleotropism or linkage of genes. The anterior pituitary has nothing to do with the sickling phenomenon and its consequences.

Julius Bauer, M.D.

1680 Vine St.
Hollywood 28, California.
January 8, 1945

ASSOCIATION NOTICE

CHANGE OF MANAGING EDITORSHIP

Dr. Roy Graham Hoskins, Managing Editor of the Journal of Clinical Endocrinology terminates his Editorship of the Journal with this issue. Dr. Hoskins' devoted and effective service to *Endocrinology* and later to the *Journal of Clinical Endocrinology* has extended over a period of 28 years.

As Editor of this Clinical Journal, Dr. Hoskins has served during the War Emergency and has performed notable service in maintaining publication standards during a period when research in this field has suffered a serious decline.

It is with keen regret that the Association accepts Dr. Hoskins' resignation, which is offered solely because of other additional responsibilities which demand his full attention.

Dr. Kenneth Wade Thompson, Associate Managing Editor, assumes the title and responsibilities of Managing Editor with this issue of the Journal. The same Editorial Board will continue to assist the new Managing Editor.

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Abstracts of
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GONADS

GUSBERG, S. B., AND D. N. DANFORTH

Clinical significance of struma ovarii. *Am. J. Obst. & Gynec.* 48: 537. 1944.

A report is presented in which thyrotoxicosis, a large struma ovarii and a huge goiter were coexistent. There is only presumptive evidence that the ovarian tumor contributed to the thyrotoxicosis. Of 297 ovarian teratomata, there were eight instances of struma ovarii, but only this one presented symptoms of hyperthyroidism.—*E.C.H.*

HISAW, F. L., M. X. ZARROW, W. L. MONEY, R. V. N. TALMAGE, AND A. A. ABRAMOWITZ

Importance of the female reproductive tract in the formation of relaxin. *Endocrinol.* 34: 122. 1944.

This investigation deals with the action of estrogen, progesterone and relaxin in experimental relaxation of the pelvic ligaments of guinea pigs. It is concluded that relaxin acts as a specific hormone, directly responsible for this reaction. Relaxin does not possess either chemical or physiological properties in common with estrogen or progesterone in that it is not soluble in fat solvents nor does it produce estrogenic or progestational reactions in experimental animals. The observations of other investigators that, under suitable conditions, progesterone will bring about relaxation of the pelvic ligaments of castrated female guinea pigs have been confirmed. However, a maximal response to one injection of progesterone was attained 72 to 96 hours after the hormone was administered, while under similar conditions relaxin produced a maximal effect within 6 hours. Also, progesterone did not produce relaxation in castrated, hysterectomized guinea pigs while the absence of the ovaries and uterus had no effect on the response to relaxin. This suggests that relaxin is absent in hysterectomized animals given progesterone. Progesterone also brought about the presence of relaxin in the blood of female rabbits. The highest concentration found in experimental animals was approximately one unit of relaxin per 5 cc. of blood serum. This concentration is the same as that found during pseudopregnancy and one-fiftieth of that for the last week of pregnancy. The amount of relaxin in the blood was not correlated with the size of the dose of progesterone nor necessarily with the length of treatment as 0.5 mg. daily for 5 days was nearly as effective as 5 mg. daily for 9 days. Relaxin did not appear in the blood of castrated male and castrated, hysterectomized female rabbits given similar treatment. This indicates that the female reproductive tract is essential for the formation of relaxin in response to progesterone.

The time intervening between an injection of progesterone and the appearance of relaxin in the blood was determined on castrated female rabbits that had been pretreated with estrogen. Following the injection of 10 mg. of progesterone, 5 cc. doses of serum, when tested for relaxin on guinea pigs, gave negative results for the 48th hour and the pelvis of only one of 20 animals relaxed when given serum taken at the end of 96 hours. When the dosage of progesterone was increased to 20 mg. a slightly positive result was obtained for the 36th hour, a good response for the 48th hour and blood taken on the 96th hour was yet definitely active. It required about the same length of time for a dose of progesterone to bring about the appearance of relaxin in the blood of rabbits as for it to produce relaxation of the pelvic ligaments of guinea pigs.

Estradiol stimulated the formation of relaxin in castrated female rabbits but not in castrated, hysterectomized females nor castrated males. Also, the effects of estrogens on the pelvic ligaments of castrate female guinea pigs greatly facilitated the action of relaxin. Furthermore,

estrogens are known to produce morphological changes in the pelvis of guinea pigs involving resorption of cartilage and bone. Therefore, pelvic relaxation, when induced by estrogens, may be due partly to these structural modifications in addition to the action of relaxin.—*Authors' Summary.*

HURXTHAL, L. M., AND NATALIJA MUSULIN

Gynecomastia. A case associated with mixed tumor of renal origin and testicular atrophy. *Lahey Clin. Bull.* 4: 38. 1944.

A case of gynecomastia associated with mixed tumor of renal origin, with extensive metastasis to the liver and testicular atrophy, is briefly described. Estrogen was demonstrated in both the blood and the urine. Gonadotropin was not detected in either fluid nor were castration cells seen in the anterior pituitary.—*R.G.H.*

MARBURG, O.

The endocrine glands in infantile amaurotic family idiocy. *J. Nerv. & Ment. Dis.* 100: 450. 1944.

The cases are reported of two boys and a girl with autopsy findings in the endocrine glands. In one case the adrenal medulla was absent and in two only a narrow remnant was seen. The adrenal cortices were normal or contained small adenomatous areas. In all three cases there was seen evidence of "prematurity and degeneration" of the interstitial cells of the gonads. The thymus glands showed cytologic evidence interpreted as indicating relative hyperplasia. The thyroids showed some degree of colloid enlargement. The hypophysis, parathyroids and pancreas were normal. On the basis of findings in these cases and others reported in the literature, the author postulates an endocrine etiology in various of the asthenias. It is suggested that the mechanism may be chiefly a disturbance in the acetyl-choline mechanism (production of choline esterase?).—*R.G.H.*

MARDER, S. N., AND W. L. MONEY

Concentration of relaxin in the blood serum of pregnant and postpartum rabbits. *Endocrinol.* 34: 115. 1944.

A standardization curve for relaxin in the blood of pregnant rabbits, showing the relationship of dosage to response, has been presented. Blood serum taken from a rabbit about the 27th day of pregnancy contained one guinea pig unit (1 GPU) of relaxin in each 0.1 cc. This is equivalent to the amount of relaxin obtained from 1 gm. of fresh corpora lutea of the sow. Relaxin was found in the blood of pregnant rabbits as early as the 3rd day after mating. The amount in the blood increased rapidly between the 12th and 24th day, a plateau being reached at the 24th day and maintained for the remainder of pregnancy. A very sharp decline occurred immediately after parturition, and the hormone practically disappeared from the blood within 3 days. Relaxin was also present in the urine of pregnant rabbits in which it appeared to be quite stable and readily assayed. It was found as early as the 5th day of pregnancy and the amount excreted in the urine increased with the progress of gestation.—*Authors' Summary.*

MARRIAN, G. F.

An androstenetriol in normal human urine. *Nature* 154: 19. 1944.

Evidence is presented to show that a steroid isolated by Hirschmann (*J. Biol. Chem.* 150: 363. 1943) from the urine of a boy with a carcinoma of the adrenal cortex is identical with the one detected by the author and G. C. Butler several years ago in normal human and human pregnancy urine.—*Courtesy Biol. Absts.*

MCGOLDBRICK, S. L., AND W. A. LAPP

Theca cell tumors of the ovary. *Am. J. Obst. & Gynec.* 48: 409. 1944.

Of 176 ovarian tumors removed surgically, three were thecomas. One thecoma was discovered incidentally at autopsy. Brief case histories are presented. No hormonal extractions were made. A short statistical analysis of 74 patients, including the authors' four patients, collected from the literature is presented.—*E.C.H.*

MEYER, A. E.

Tropic or trophic? *The Lancet*, 247: 454, 1944.

The etymology of the expressions gonadotropic and gonadotrophic is discussed. The Greek word trepein signifies "to turn toward" or "to aim at." Accordingly, a poison directed against the nervous tissue is called neurotropic, a plant that turns toward the sun is heliotropic. Ehrlich used similarly the words bacteriotropic and organotropic to characterize the direction of affinity of chemical substances. Gonadotropic, applied to the pituitary hormone, means the substance having a

characteristic effect on the gonads without specifying the nature of this action. A stimulation of growth, change in structure or inhibition are equally covered by this expression. Trephein, from which trophic is derived, means to nourish, make grow or nurture. This function is more adequately applied to the nourishing blood supply than to a hormone, the effect of which in certain conditions is an actual decrease in size of the ovary, or a structural change without growth. Still more difficult is the application of "trophic" to the chorionic material that, although influencing the gonads, is by no means the natural hormone producing maturity of the gland. It is therefore recommended to use exclusively the undescriptic "tropic" because it does not carry any commitment concerning the mode of action of the substances.—Carnegie Dickson, W. E. *ibid.*, p. 518. The considerations given in the preceding article are supported. It is pointed out that tropic, meaning "turning towards" permits a general application whereas trophic applied to the analogous series of expressions "dermotropic" and "neurotropic" in connection with certain viruses would suggest that the viruses nourish the skin or nervous system.—*A.E.M.*

MILLAN, JUSO MAXIMO AND ARCADIO C. BARAÑO

Contribution to the hormone treatment of cancer. *Semana médica*: 51, II: 627, 1944.

A number of patients with malignancies in various organs (7 cases reported in detail) were subjected to a study of hormone excretion and hormone treatment. The following conclusions were drawn: the gonadotropin content in the blood and urine of cancer patients is augmented. This increase is not in proportion with the severity or progress of the ailment. The estrogen excretion is unchanged. Therapy aiming at pituitary block with estrogens, thyroid hormone or x-rays caused in every case a light improvement although the progress of the disease was not changed. The Friedman reaction may be positive in cancer patients disregarding the site of the tumor, but is usually too weak to be of diagnostic value.—*A.E.M.*

MILLER J. R.

Preoperative use of testosterone propionate as an aid to the surgical treatment of endometriosis. *J.A.M.A.* 125: 207. 1944.

A case is reported of a large endometrioma involving the rectum in which 25 mg. of testosterone proprionate was given twice weekly for three months before operation. After two months the mass appeared by palpation to have decreased to one-third of its original size but there was little or no further decrease during the third month. Systemic effects were minimal. Menstruation after one month of treatment was not abnormal but after two months treatment was delayed and not accompanied by the usual cramps and diarrhea. The histological appearance of the endometrioma removed at operation is not described in detail. References are given to reports of similar cases.—*A.P.F.*

NOVAK, E.

Post-menopausal bleeding as a hazard of diethylstilboestrol therapy. *J.A.M.A.* 125: 98. 1944.

This is a discussion of what constitutes safe and adequate treatment of the menopause with estrogens. It is the author's view that the dose of any estrogenic substance used should be held to the minimum which will prevent severe vasomotor symptoms. He feels that full replacement therapy is undesirable for the following reasons: 1. The patient becomes dependent on the drug and fails to adjust to the lack of endogenous hormone. 2. The occurrence of withdrawal bleeding may lead to a suspicion of uterine cancer and hence to unnecessary curettage. 3. The failure to interrupt treatment regularly may lead to bleeding from a hyperplastic endometrium. 4. The administration of large doses of estrogen to patients with a predisposition to cancer might further the development of a malignant growth. He believes that treatment should be withdrawn as rapidly as consistent with the patient's comfort.—*A.P.F.*

SCHILLER, J., AND G. PINCUS

The metabolism of estrone in normal and partially hepatectomized rats. *Endocrinol.* 34: 203. 1944.

The phenolic fractions of the pooled urines of groups of 7 to 10 male rats were divided into non-ketonic weak phenols (estradiol), ketonic weak phenols (estrone) and strong phenols (estriol). These three fractions were assayed for estrogenic activity in urine collected before and after partial hepatectomy and before and after the injection of 50 micrograms of estrone per rat.

The estrogen assay data indicate that normal male rats effect the conversion of injected estrone to non-ketonic weak phenolic and strong phenol-

ic estrogen. On the assumption that the activity of the three phenolic fractions is ascribable to α-estradiol, estrone and estriol, 18.7% of the estrone injected into normal male rats can be accounted for in the urinary excretion for 4 days following injection. The urinary estrogen excreted by the normal male rats after estrone injection appears to be free, not esterified.

The endogenous estrogen excreted into the urine following partial hepatectomy increases in amount particularly in the non-ketonic weak phenolic fraction. After estrone injection into hepatectomized male rats the urinary estrogen titers increase markedly. It may be calculated that 65.5% is recovered in terms of urinary metabolites.

While hepatectomy leads to increased estrogenic activity in all phenolic urine fractions after estrone injection, the strong phenolic estrogen increases a little over two times, the weak phenolic non-ketonic approximately four times and the weak phenolic ketonic nearly six times in a 96-hour collection period. This is taken to indicate that the conversion of estrone to estriol is most markedly interfered with by liver lobe extirpation.—*Authors' Summary.*

SHUTE, E.

On the oestrogenic origin of uterine fibromyomas. *Canad. M.A.J.* 51: 443. 1944.

The author studied the histories of 130 women between the ages of 22 and 57 having fibromyomas. Of these, 52 per cent gave a history of menorrhagia, probably functional, in the second decade. Also 63 per cent exhibited signs and symptoms of hypothyroidism, according to their histories. In view of the supposed relationship of fibromyomas and estrogenic activity, the author suggests that the use of anti-estrogens such as thyroid may be used prophylactically. He suggests that the control of functional menorrhagia in the earlier decades might have prevented the organic menorrhagia which developed later.—*P.H.S.*

SMILEY, I., AND J. I. KUSHNER

Ovarian pregnancy. *Am. J. Obst. & Gynec.* 48: 543. 1944.

The authors present a case of ovarian pregnancy which fulfills the requirements of Spiegelberg and was thought to be intrafollicular (fecundation within the follicle) in type.—*E.C.H.*

SMITH, A. AND R. ST. JOHN

Council on pharmacy and therapy, *J.A.M.A.* 125: 786. 1944.

The following dangers attending the use of endocrine products are listed:

I. Thyroid, 1. Production of thyrotoxicosis. 2. Precipitation of Addisonian crisis in patients with "pituitary myxedema." 3. Heart failure in patients with coronary disease.

II. Estrogens, 1. The stimulation of preëxisting cancer. 2. Production of hyperplastic endometrium with excessive or irregular flowing. 3. Inhibition of ovulation in women of childbearing age.

III. Testosterone, 1. Masculinization in the female. 2. Premature closure of the epiphyses in children. No mention is made of the dangerous effect of testosterone on carcinoma of the prostate.

IV. Gonadotropins, 1. Pituitary and equine gonadotropins may be antigenic 2. According to the author chorionic gonadotropin is of little value except in the treatment of undescended testes.

V. Pituitary growth hormone and posterior pituitary products, 1. Hypersensitivity due to the antigenic properties of the extract constitute the chief danger.—*A.P.F.*

SONTAG, L. W., E. R. REYNOLDS AND V. TORBETT

The relation of basal metabolic gain during pregnancy to nonpregnant basal metabolism. *Am. J. Obst. & Gynec.* 48: 315. 1944.

The relationship between nonpregnant basal metabolic level and the basal metabolic gain during pregnancy was investigated in 158 women. Those women who had the lowest nonpregnant basal metabolic rates tended to have the greatest pregnancy gain. Nearly 45 per cent of the women had nonpregnant basal metabolic rates below −10 per cent.—*E.C.H.*

THOMPSEN, W. C.

The clinical use of extracts from the testis and of synthetic products having similar actions. *J.A.M.A.* 125: 15. 1944.

This is a practical article which gives specific directions as to the choice of gonadotropic and androgenic therapeutic agents, their dosage and the established indications for their use. Treatment is outlined for the following conditions: 1. Undescended testes and hypogonadism second-

ary to hypopituitarism (including Fröhlich's syndrome), treated with chorionic gonadotropin. 2. Primary hypogonadism and secondary hypogonadism which does not respond to gonadotropin treated with testosterone.—*A.P.F.*

TRAFTON, H., AND H. J. PERKIN

The clinical significance of serum acid phosphatase with especial reference to carcinoma of the prostate gland. *Lahey Clin. Bull.* 4: 59. 1944.

A study of 50 cases of carcinoma of the prostate gland showed an elevated serum acid phosphatase in 24 cases (48 per cent). In 22 cases the serum alkaline phosphatase was elevated, and in 17 cases both phosphatases were elevated; in the group of 21 cases with bony metastases the acid phosphatase elevation was most closely correlated. Eighty-one per cent showed an initial elevation, the highest being a value of 34.0 units. In 24 patients having initially elevated serum acid-phosphatase values, castration in every case was followed by a pronounced fall in the level within 24 to 48 hours. There was often a transient secondary rise of small degree, followed by gradual decline until an equilibrium was reached after about two months. After an interval of one to three years, the majority of cases again showed an elevation of varying amounts. This secondary rise correlated fairly well with clinical evidence of recurrence of carcinoma and seemed to be only slightly reduced by treatment with stilbestrol. It was concluded that an acid phosphatase of 0.8 to 1 unit, especially when the alkaline phosphatase is normal (thus ruling out Paget's disease, etc.) warrants a suspicion that the patient has metastasizing carcinoma of the prostate. An acid phosphatase of 1.2 units or more may be considered pathognomonic of carcinoma with bony metastases, especially if the alkaline phosphatase also is elevated. On the other hand, a normal acid phosphatase is no assurance that metastases are not present, especially in the undifferentiated types of carcinoma. In addition to the diagnostic value of the phosphatases, they are valuable from a prognostic standpoint in the clinical follow-up period, in that they serve as a guide to additional endocrine therapy.—*R.G.H.*

VIERGIVER, E., AND W. T. POMMERENKE

Measurement of the cyclic variations in the quantity of cervical mucus and its correlation with basal temperature. *Am. J. Obst. & Gynec.* 48: 321. 1944.

The amount of cervical mucus was measured by aspiration into a weighed glass cannula. Observations were made throughout the menstrual cycle in 4 married nulliparous women. Correlation with basal vaginal temperatures were made during 7 cycles. About 60 milligrams or less of mucus was obtained from the end of bleeding to about the eighth or ninth day. Then, a peak secretion of from 200 to 700 milligrams occurred for about 4 days. This was followed by a sharp decline to the previous level of 60 milligrams or less, and remained there throughout the rest of the cycle. In 6 of 7 cycles, the maximum secretion preceded the rise in temperature by one to three days. In the seventh cycle, the maximum secretion and temperature shift occurred on the same day.—*E.C.H.*

WENGRAF, F.

Psychodynamic and therapeutic aspects of functional dysmenorrhea. *Am. J. Obst. & Gynec.* 48: 475. 1944.

The author considers functional dysmenorrhea as a symptom complex associated with menstruation which affects, in addition to the pelvic organs, the personality as a whole. Only a partial description of the psychologic aspect is given. Four case reports illustrate the relationship between dysmenorrhea and neurosis.—*E.C.H.*

HYPOPHYSIS

CHAPMAN, A., AND G. M. HIGGINS

Role of the thyroid in the cytologic response of the pituitary to low intake of iodine. *Endocrinol.* 34: 83. 1944.

The cytologic changes in the pituitary gland have been described in intact and in thyroidectomized rats maintained on diets containing high and low levels of iodine. The characteristic cellular patterns in the pituitaries of these 4 groups were compared. Among nonthyroidectomized animals maintained on a low intake of iodine there were: a) an increase of the number and size of the basophilic cells in the pituitary glands, b) an increase of the size of their nuclei and the Golgi apparatus, and c) an increased deposition of colloid by the basophilic cells when contrasted with the pituitaries of animals receiving adequate amounts of iodine. Among thyroidectomized animals maintained on a high intake of

iodine there were: a) a decrease of the number of eosinophilic cells, and b) a degranulation of the cytoplasm of the chromophilic cells of the pituitary. There were large deposits of colloid associated with eosinophilic cells. Among thyroidectomized animals maintained on a low intake of iodine there was a generalized cytoplasmic degranulation of both series of chromophilic cells; large deposits of colloid were associated with these degranulated cells.—*Authors' Summary.*

HEINBECKER, P.

Pathogenesis of Cushing's syndrome. *Medicine* 23: 225. 1944.

Heinbecker presents clinical studies in 6 cases of Cushing's syndrome as well as experiments on dogs. In 5 of the cases the hypothalamus was available for study. Hyalinization of basophil cells was found in all 5. In 4 changes in the hypothalamic nuclei, particularly the paraventricular nuclei, were noted. In none of these 4 was an adrenal tumor present. In the fifth case, in which a malignant adrenal tumor was found at necropsy, no hypothalamic lesion was present. In the sixth case an adrenal tumor was removed at operation but the brain was not available for study. Dogs with an experimental lesion of the hypothalamus involving areas similar to those found involved in 4 cases exhibiting Cushing's syndrome show definite loss of basophil cells, with degenerative changes in the remaining basophil cells in the hypophysis. In such animals changes occur in the thyroid, in the gonads and in the islets of the pancreas of a type which serves to explain many of the symptoms of Cushing's syndrome. Experimental evidence is offered to show that at least two of the primary lesions could be expected to cause a disturbance of lipid metabolism characterized by an accumulation of fat and cholesterol in the adipose tissue of certain regions of the body. In dogs with complete or partial bilateral destruction of the caudal portions of the paraventricular nuclei there is just such an infiltration of fat and cholesterol into tissues such as the skin, the muscles, the liver and the walls of the blood vessels as occurs in persons exhibiting Cushing's syndrome. The author thinks that the conclusion now seems permissible that either an adrenal tumor or hypofunction of the paraventricular hypothalamic nuclei may be primary causes of the basophil degeneration which in turn is the immediate cause of many of the typical findings of Cushing's syndrome. Evidence is presented to suggest that the hypothalamic dysfunction may lead to hyalinization of the basophil cells through an increased effectiveness of the hormone secreted by the adrenal cortex. In this way a common pathway for influencing the hypophysis is found for the various primary disturbances which lead to Cushing's syndrome.—*Abst. J. Am. M. Assn.*

RYNEARSON, E. H.

Hormones of the anterior lobe of the pituitary body. *J.A.M.A.* 125: 5. 1944.

The author has searched the literature for careful reports of clinical trials of various pituitary products and finds: 1. That growth hormone has occasionally been proved effective but has seldom been tried without thyroid and other agents which promote growth. 2. Thyrotropic hormone has been shown to raise the B.M.R. in the presence of a functioning thyroid gland. 3. True pituitary gonadotropins are not yet available in safe preparations. 4. Prolactin, the one crystalline pituitary hormone so far available for clinical use, will promote lactation in some cases. 5. Antihormone production commonly results from the injection of pituitary products and probably explains many clinical failures.—*A.P.F.*

TORDA, CLARA, AND H. C. WOLFF

Effect of adrenotrophic hormone of pituitary gland on ability of tissue to synthesize acetylcholine. *Proc. Soc. Exp. Biol. & Med.* 57: 137. 1944.

The authors tested a theory that the symptomatology of myasthemia gravis may be due to defective acetylcholine synthesis by noting in mice the effect of adrenotropic hormone. The brains of mice so treated for 15 days synthesized on the average 50% more acetylcholine than did those of control animals.—*R.G.H.*

PANCREAS

COLWELL, A. R.

Nature and time action of modifications of protamine zinc insulin. *Arch. Int. Med.* 74: 331. 1944.

The author concludes this very practical contribution as follows: The activity of standard protamine zinc insulin is spread out too thin for most efficient once-daily use in cases of diabetes mellitus. Hence it permits glycosuria and hyperglycemia after meals, causes hypoglycemia during fasting, is too unpredictable in its overlapping

effects and requires supplementation with ordinary insulin either by separate injection or by admixture. Because it is an insulin-unsaturated compound, mixtures made from it may be deceiving by not reflecting directly small amounts of insulin added to it. The protamine and zinc now used in the preparation of protamine zinc insulin can combine 2½ to 3 times as much insulin in buffered preparations and more when slightly acid. A saturated compound combines 250 to 300 instead of 100 units of insulin per milligram of protamine and 0.2 mg. of zinc at pH 7.2. It has a monophasic action in which it releases insulin at a more rapid rate than standard protamine zinc insulin. Therefore it is ideal for morning injection once daily because it controls glycosuria following meals better, is less likely to cause hypoglycemia during fasting, is more predictable in action and does not require supplementary insulin when used with diets of moderate carbohydrate value. When it is desirable to supplement it, added insulin is reflected directly in increased rapid effect. It is stable and practically free from allergic effects. The action of globin zinc insulin is too quick and intense and not sustained enough for once-daily subcutaneous injection in cases of severe diabetes. Its supposed advantage of homogeneity by virtue of packaging in acid solution is a disadvantage instead, because its time action depends on the completeness of its precipitation on alkalinization after injection. Any protamine zinc insulin modification could be marketed in solution, but it is doubtful that that is desirable. A single intermediate modification should be selected on the basis of greatest efficiency for the average diabetic patient. If prolonged enough in action it could replace standard protamine zinc insulin and not confuse the problem by addition of another insulin to the market. Modification of it would usually not be necessary with diets of moderate value. Adjustments in the distribution of food would accommodate to most variations in response of individual diabetic patients.—*Author's Conclusions.*—*I.B.*

HOUSSAY, B. A.

Diabetes during and after thyroid feeding. *Rev. Soc. Argentina Biología*: 20: 179. 1944.

Thyroid feeding has no influence on the blood sugar in the normal dog. It causes diabetes if the pancreas has been removed to a residue of 2.5 to 3 gm. Previous treatment with pituitary extract renders the animal more sensitive to thyroid. Such diabetes may persist after cessation of thyroid administration. The diabetes is characterized by reversible or non-reversible lesions of the β cells of the pancreas. Insulin protects the pancreas in the early period of the lesions, but not later. The "metathyroid" diabetes may develop in absence of the gonads, the thyroid and the adrenal medulla. Hypophysectomized and adrenalectomized dogs do not develop hyperglucemia on thyroid treatment; on the contrary, the latter die with hypoglucemia during thyroid treatment. Metathyroid diabetes has the same characteristics as common pancreatic diabetes.—*A.E.M.*

JOHN, H. J.

The differential diagnosis of glycosuria. *Am. J. Dig. Dis.* 11: 313. 1944.

The author discusses the significance of glycosuria and reports a series of 16 cases, in 12 of which the phenomenon was of non-diabetic origin. He emphasizes that the differential diagnosis between diabetic and non-diabetic glycosuria can be made only by a glucose-tolerance test or by a blood-sugar estimation two and a-half hours following a heavy carbohydrate meal. Numerous urine estimations for sugar for diagnostic purposes settle nothing and waste time. Non-diabetic glycosuria is not a precursor of diabetes. The renal threshold in a non-diabetic glycosuric is usually low. It varies on the ascent and descent of the sugar curve, being higher on the former and lower on the latter. Upon the finding of glycosuria, a prompt diagnosis should be made. This will eliminate the possibility of self-imposed dietary restrictions which distort the glucose tolerance curve (toward the diabetic side) which thus tends to give misleading information. There is no treatment for non-diabetic glycosuria and none is needed.—*R.G.H.*

LUKENS, F. D. W., AND DOLAN. F. C.

Remissions of diabetes mellitus. *Pennsylvania M. J. 48*: 24. 1944.

Of a total of 517 diabetics 19 who showed striking improvement for periods of 1 month to 10 years were selected and the nature of their remissions was described. Seventeen of these were treated within the first 4 months of the disease thus indicating the value of early treatment. Such improvement may be a result of regeneration of the damaged islands of Langerhans, to a reduction in the requirement for insulin, or to the increased efficiency in the action of insulin. —*I.B.*